Biological Science and Biotechnology in Russia: Controlling Diseases and Enhancing Security

Committee on Future Contributions of the Biosciences to Public Health, Agriculture, Basic Research, Counter-terrorism, and Non-Proliferation Activities in Russia, Office for Central Europe and Eurasia, National Research Council

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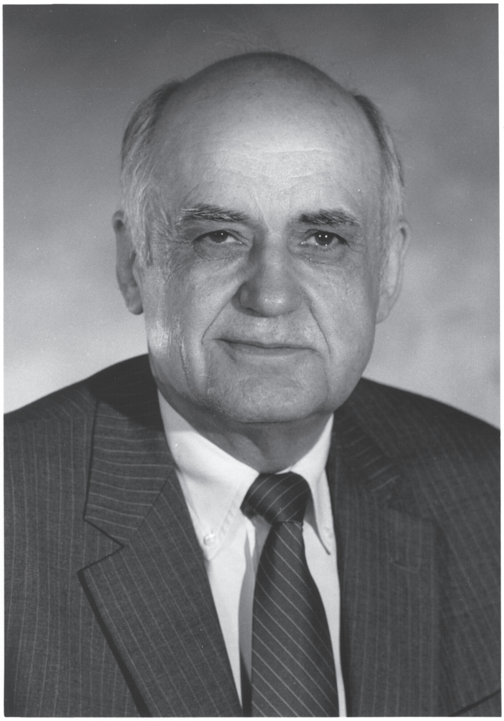

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Humanitarian, Colleague, Mentor, and Friend
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[1]Deceased April 11, 2005.

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by Mary Jane Osborne, University of Connecticut, and Patricia Danzon, University of Pennsylvania. Appointed by the NRC, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

In addition to the formal reviewers of the report, there were many who offered their time and expertise over the course of the study's development. The committee wishes to express its appreciation to all those who contributed. In particular, Michael Balady, James Bartholomew, Randy Beatty, Anne Harrington, Lev Sandakhchiev, Vladimir Skulachev, Mark Smolinski, Rob Tosatto, and Vitaly Zverev participated in a series of meetings and discussions which transformed initial thoughts into the first draft of this manuscript during a productive July 2003 week in Woods Hole, MA. Sergey Furgal, Yevgeny Grishin, Ramil Khabriev, Sergey Netesov, Mikhail Paltsev, Evgenii Severin, and Nikolai Vlasov, along with their colleagues, shared many valuable insights with members of the committee during their several research trips to Russia undertaken as part of this study. They frequently provided hard-to-find data, regulations, and information upon which the committee's analysis was based; their openness and frankness were offered in the best spirit of international science. The final trip was to St. Petersburg in July 2004, when the committee had the opportunity to meet again with many of these Russian colleagues. Undoubtedly there are those who are inadvertently absent from these acknowledgements. The committee recognizes that without the efforts and professionalism of those named and unnamed, this and other cooperative work between Russia and America could not be accomplished.

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Summary

INTERNATIONAL INTEREST IN RUSSIA'S CAPABILITIES TO COMBAT INFECTIOUS DISEASES

A concerted global effort is needed to combat both naturally occurring and intentionally introduced infectious disease agents. Russia, with its vast ecological diversity and large, well-trained scientific workforce, should be a leader in efforts to prevent, detect, and respond to the emergence and resurgence of infectious diseases at home and abroad.

The international community clearly recognizes that disease-related developments in Russia have profound global implications. Many Western countries have therefore initiated cooperative programs in Russia aimed at preventing the proliferation of biological materials and expertise to countries with hostile intentions. Other international efforts have been directed toward countering the possibility of terrorist groups acquiring biological capabilities. Still other programs have been driven by the conviction that shared scientific expertise leads to mutual benefits in the broader effort to improve public health. Thus, the importance of cooperative efforts for both Russia and its partners has been widely recognized. In addition to cooperative programs, the Russian government has developed a conceptual framework for strengthening the country's public health system. Relevant ministries also are well aware of the need to improve the means of combating agricultural diseases, promote research and development, and support the emergence of biotechnology firms. However, because implementation of such concepts continues to be severely constrained financially, international financial support will continue to be important.

In 2003, a committee of the National Research Council (NRC),[1] building on a decade of experience promoting U.S.-Russian engagement in biological research and in close consultation with Russian colleagues, initiated a study that would set forth a realistic vision for the development of the biosciences and biotechnology in Russia over the next ten years. Further, the committee considered practical steps that could be taken by Russia, independently or collaboratively with international partners, to move toward the achievement of that vision.

The specific charge to the NRC committee responsible for this assessment was as follows:

> This project will present a 5 to 10 year vision of an environment in Russia for biological research and production activities that encourages efforts to prevent bioterrorism and the proliferation of potentially dangerous biological agents and expertise while addressing public health, agricultural, industrial, environmental, and scientific challenges. The project will address both: (1) the positive contributions to peaceful science, economic, and social development that can be made by biological institutions; and (2) the possibilities of misdirection of materials and expertise to terrorist groups or to states seeking biological weapons capabilities. Also, the project will suggest near-term steps that can be taken by the Russian government, by Russian institutions, and by the international community to contribute to the development of such an environment. U.S.-Russian cooperative programs will receive special attention, since during the past several years they have played a key role in reducing the likelihood of bioleakage (the spread of biological materials and expertise) from Russian institutions.

Thus, the report should be of interest to officials and specialists in both Russia and the United States and also to the broader scientific community around the world.

A VISION FOR STRENGTHENING PUBLIC HEALTH AND SECURITY

Of primary importance is the evolution of a stronger, more flexible public health system in Russia that is increasingly integrated into global networks as they respond to endemic and emerging diseases. These enhanced capabilities could contribute to a significant reduction of vaccine-preventable and drug-curable infections in both humans and animals in Russia, which would include: (1) more effective utilization of disease prevention measures; (2) increased effectiveness at national and local levels in controlling arthropod vectors and animals that serve as reservoirs for zoonotic diseases; and (3) a more effective global approach to combating infections through stronger and more active cooperation with international partners.

[1]See Appendix A for committee biographies.

To achieve this goal, the committee recommends strengthening Russian policies and programs by:

- focusing on surveillance, laboratory diagnostics, and development of countermeasures (e.g., drugs and vaccines) capable of addressing diseases in the broadest sense
- improving capabilities to detect and diagnose new, reemerging, and antibiotic-resistant pathogens in both rural and urban settings, including upgraded communication systems to provide timely and accurate information
- integrating human and animal disease surveillance
- monitoring food and water supplies for safety and potability
- supporting well-focused research projects that strengthen the base of fundamental scientific knowledge
- strengthening programs to commercialize scientific findings within a regulatory framework that supports public health and protects agriculture
- developing an improved understanding of the relationships between infectious agents and important non-communicable chronic diseases, a priority of growing global interest
- supporting the emergence of a strong domestic biotechnology sector that enhances efforts to combat infectious diseases affecting the Russian population
- developing and implementing effective security procedures at hundreds of facilities that can propagate, store, or distribute pathogens which, if diverted, could be used for bioterrorism; an important initial step would be to conduct a careful nationwide inventory of strains and consolidate many collections where appropriate
- promoting broad transparency of Russian research and other public health prevention and control activities involving dangerous pathogens, in order to reduce international apprehensions regarding the possible misuse of Russian research or the unauthorized diversion of infectious agents; comparable transparency would also be expected in other countries
- recruiting, training, and retaining an expanded cadre of biomedical scientists, medical doctors, veterinarians, plant pathologists, epidemiologists, and other relevant specialists equipped with modern technology and positioned to deal with infectious disease threats

Russia has the government institutions, legal framework, technical expertise, human resources, and distinguished tradition of scientific excellence needed to support these developments. But there is an urgent need to strengthen Russia's recently reduced capabilities in many areas. Fortunately, the economic situation in Russia is slowly improving, and the implementation of effective health and agricultural policies is much closer to being achieved than it was just two or three years ago. In particular

- the Russian leadership is coming under increasing pressure from politicians and the public as the consequences of deteriorating public health—unproductive workers, unfit military conscripts, debilitated pensioners, and underachieving children—become increasingly apparent
- Russian investments in health-related programs are increasing, and Russian research institutions are now successfully competing for external resources
- as Russia's economy improves, its embryonic biotechnology industry is charting an ever more optimistic course and is beginning to achieve success
- sensitivity within the Russian government to the dangers of bioterrorism, as well as recognition of the steps needed to reduce this threat, are rising

This report sets forth four key themes, or pillars, for countering infectious diseases in Russia. They represent the committee's view of priority areas for development over time.

FOUR PILLARS FOR COUNTERING INFECTIOUS DISEASES

Pillar One: Improving Surveillance and Response

Over the long term, enhanced surveillance capabilities in Russia would improve the country's ability to: (1) determine the incidence and prevalence of endemic and emerging diseases in humans, animals, and plants; and (2) detect and identify infectious agents within a national reference laboratory system that is connected to the global system of the World Health Organization. This will require a strong, state-of-the-art capacity to investigate disease outbreaks, which builds on Russia's long history of successful epidemiology and disease surveillance.

Specific suggestions for achieving this goal are set forth below. The committee recognizes, however, that there are other dimensions of surveillance that also deserve consideration, particularly in the area of animal and plant monitoring.

- *Establish two model State Sanitary Epidemiological Surveillance Centers (SSESCs) for surveillance, diagnosis, analysis, and communication of information concerning infectious disease episodes.* One center would be at the regional (oblast) level, and a related one would be at the local level within the same region. It is recommended that these model centers be placed in a region where financial resources have traditionally been less plentiful, most likely in a region distant from Moscow or St. Petersburg. This would be an important step in establishing standards that could serve as a model for upgrading the entire SSESC network over the long term. Because SSESCs are the primary organizations for reporting disease trends and outbreaks, particularly at the local level, they are also an important resource for surveillance oversight in Moscow.

The model centers should be internally linked via electronic communications with SSESCs throughout the country, and externally with the World Health Organization and other member nodes of the international disease surveillance community. The model centers could provide training and have surge capacity to address outbreaks and other crisis situations not only in their own geographical areas but also in nearby regions of the country while also providing up-to-date information to Moscow. Regardless of the locations of the model centers, significant investments will be required to: (1) establish them either through upgrading existing facilities or constructing new facilities; and (2) upgrade additional centers based on lessons learned at the model centers.

- *Integrate Russia's anti-plague network fully into the national public health surveillance system and then into global systems.* Even though the Russian anti-plague monitoring facilities have largely remained isolated from the international community, perhaps due to security sensitivities dating from the Soviet era, they continue to be an essential component of Russian efforts to prevent and control infectious diseases of local, national, and global interest. Their data banks and their strain collections are valuable resources and should be fully drawn upon when building modern disease prevention and control programs that include geographic monitoring, laboratory diagnosis, reference identification, and intervention. Transformation from an internal to an external orientation could begin with modest investments to update disease surveillance within Russia, first by strengthening the equipment and communication capabilities of the five anti-plague institutes, and then by initiating international cooperation.

Pillar Two: Meeting Pathogen Research Challenges

Focusing laboratory research, and the resources to support that research, would help Russia advance public health and control agricultural diseases more effectively. Two related suggestions for achieving this goal are as follows:

- *Concentrate financial support at carefully selected research groups that are, or have the potential to become, centers of scientific excellence.* Several hundred key Russian laboratories, each of which employs one or more integrated groups of scientists working toward common goals, are, or could be, essential core elements of the Russian public health and agriculture research infrastructures in the future. These important laboratories warrant special financial support provided through a competitive peer review process to enhance the programs of their research groups. Criteria for determining special financial support might include: (1) scientific excellence and relevance of research activities to public health and agriculture priorities of the Russian government; (2) recent achievements of the research groups in advancing specific areas of science and in contributing to important human, animal, and plant disease prevention and control programs of the Russian government; (3) demonstrated capabilities of the laboratory scientists, particularly the rising scientific leaders within the research groups; and (4) a tradition of cooperating with, and facilitating the development of, other Russian research groups that share research interests.

• *Upgrade laboratory facilities and equipment for appropriate infectious disease-related research at selected laboratories throughout the country.* Recent emphasis in Russia on using limited research funds primarily to meet payrolls has been accompanied by a dramatic decline in facility and equipment assets at research institutions, including the ability to maintain and disseminate data and to communicate rapidly both domestically and internationally. In turn, this erosion of equipment capabilities has resulted in a loss of competitiveness in the search for international financial support as well as a decline in research productivity. Meanwhile, many of the best Russian researchers have, out of frustration, emigrated to foreign laboratories where they can work using modern equipment. Costs of adequately equipping even the several hundred research units identified as centers of excellence will be very high, and the primary source of funds must be the Russian government. Therefore, considerable attention should be given to establishing a fair and open competitive process for selecting the recipients of funding. This process should lead to a concentration of resources to support the equipment needs of the strongest research groups. Training could also be a component of such programs to ensure optimum use of equipment.

Pillar Three: The Promise of Biotechnology

Facilitating the development of an internationally competitive biotechnology sector would also enable Russia to more fully support the control of infectious diseases. To this end, Russia needs an innovation system that encompasses all aspects of the process from start to finish: from basic molecular biology through applied research and development; intellectual property and regulatory systems; scale-up and production capabilities; commercial financing and manufacturing capabilities; and marketing and product distribution expertise.

Specific suggestions for achieving this goal are as follows:

• *Develop a business environment that encourages investment in biotechnology activities in Russia.* In particular, the following factors will encourage domestic or foreign investors to risk their capital in Russia: consistent tax policies, intellectual property rights that reward scientific success, streamlined procedures for licensing facilities and approving products, and the continuous availability of initial funds. In some cases, government cost-sharing may be warranted during a transition period. In short, the Russian government should recognize the unique challenges faced by the biotechnology sector and take specific steps to help support the emergence of a vibrant and sustainable core of biotechnology firms. Among those firms may be some linked to well-established research institutes that are, or in time will become, internationally competitive.

• *Promote investment in biotechnology niches that are well suited for activities based in Russia.* Some market niches for Russian firms have not been fully exploited. One approach the Russian government may take to promote investment is to encourage the local production of some items which are currently imported. For example, the development and enforcement of government procurement policies that favor high-quality Russian-made products at competitive prices could be very helpful in the short term. A complementary approach is for Russian manufacturers to target markets for products such as diagnostic kits and other relatively straightforward technologies in the countries of the former Soviet Union, where longtime connections give Russian firms a considerable advantage over foreign firms trying to penetrate these markets.

Pillar Four: The Human Resource Base

Nurturing a new generation of young scientific leaders in the basic and applied sciences and technologies is essential to the advancement of infectious disease prevention and control.

Specific suggestions for reaching this goal are as follows:

• *Encourage postdoctoral scientists to remain in Russia as practicing scientists through mentoring programs that prepare them for positions of leadership in various fields that support the control of infectious diseases*. There is now a shortage of biological scientists in the 30- to 45-year-old age range with important knowledge and skills related to infectious diseases. A positive step toward overcoming this trend has already been taken by the Russian government on a small scale through a limited number of federal grants designated for young scientists. Another approach that might have a greater effect is for both the Russian government and Western governments to provide financial support to those institute directors who are also prepared to use their institute's resources on a matching basis to provide improved working conditions and scientific challenges. This will help ensure an increased flow of young talent into permanent research and related positions. Also, a program of re-entry grants might encourage young scientists to return to Russia upon completion of training abroad.

• *Continuously expand the professional competence of specialists in fields related to infectious disease, particularly enhancing their ability to address multidisciplinary challenges through advanced training programs.* Advanced training could be offered at the leading national and regional research and monitoring centers, and particularly at the two model centers recommended earlier. In some cases, Russian specialists have fallen behind simply because they have not had modern equipment and broadband access to the Internet. In other cases, they have been isolated from international developments, and their skill levels have suffered accordingly. Training should, to the extent possible, provide opportunities for visits and hands-on experience at international research and monitoring centers where Russian specialists could become familiar with work at the cutting edge of science.

MODIFYING THE APPROACH TO BILATERAL COOPERATION

Involvement by the United States in Russia's biotechnology sector has largely been driven by U.S. priorities, which are to: (1) prevent the proliferation of dual-use expertise, technologies, and organisms to countries and groups with hostile intentions; and (2) redirect former Soviet bioweapon scientists and engineers to civilian activities, particularly in the areas of human health, agriculture, and environmental protection. In addition, U.S. bilateral and other foreign assistance efforts in the health and agricultural sectors have focused on controlling diseases of particular concern in Russia, such as tuberculosis, HIV/AIDS, and viral hepatitis. Several western firms have made small investments in biological activities in Russia; others have entered into short-term contracts with Russian scientists. Finally, several international foundations have supported biomedical projects relevant to infectious diseases in Russia. However, much more needs to be done in light of new challenges and new opportunities for cooperation.

The following three initiatives are designed to improve the effectiveness of cooperation in bioscience and biotechnology in order to achieve both Russian and U.S. objectives:

- *Establish a bilateral U.S.-Russian intergovernmental commission on the prevention and control of infectious diseases.* An emphasis on cooperative programs that address infectious diseases of global significance to human and animal populations of Russia and the United States, and particularly diseases of special importance in Eurasia, could be a very important focus of initial cooperation. The U.S.-Japan program, begun in 1965, could serve as a model for the commission. Subgroups of the commission might be established to consider the following topics: (1) epidemiology and surveillance of emerging diseases; (2) laboratory sciences, including detection, diagnosis, identification, and reference systems; (3) information systems and technologies; (4) biosafety and biosecurity; (5) advanced training; and (6) promotion of collaborative scientific relationships. Initially, financial support for activities of the commission and the projects it endorses would have to come largely from the U.S. government. But a near-term goal would be for each side to cover its own costs during meetings and at the bench. An early task for the commission could be to consider the recommendations presented in this report and the contributions of existing bilateral cooperative efforts in implementing the recommendations.
- *Complete the integration of former Soviet biodefense facilities that are no longer involved in defense activities into the civilian research and production infrastructure of the country.* A specific suggestion for achieving this goal is to increasingly involve in nonproliferation programs those Russian specialists who

did not participate in defense activities but who have important expertise related to disease prevention and control.

- *Focus U.S. and other western programs on establishing true partnerships in Russia.* Two specific steps toward achieving this goal are to: (1) increase the role of Russian scientists and science administrators in designing cooperative programs and projects; and (2) increase Russian financial contributions to cooperative programs as a key to sustainability and as evidence that the programs reflect Russian national priorities.

Collectively, the recommendations in this report could help restore Russia's ability to join with the United States and the broader international community in leading an expanded global effort to control infectious diseases. The proposed bilateral intergovernmental commission can play a pivotal role toward this end.

Introduction

THE CONTEXT FOR THIS REPORT

Rapid advances in biological science and technology have led to new and improved medications and medical procedures, new and safer foods, and new and diversified energy sources that are revolutionizing the way people live. The desire of nations to develop capabilities to participate in this revolution is unbounded. At the same time, there is a growing global challenge to ensure that biological capabilities are directed toward the betterment—and not the malicious detriment—of the lives of people throughout the world.

Meanwhile, infectious diseases continue to threaten human health and agriculture. Every day, tens of thousands of people throughout the world die from infections. As the recent outbreak of severe acute respiratory syndrome (SARS) so dramatically demonstrated, deadly diseases can spread rapidly around the world. All nations need to work together to prevent disease pandemics and to respond vigorously when outbreaks occur. Russia can be among the leaders in the global effort to avoid such catastrophes.

Since the disintegration of the Soviet Union in 1991, U.S.-Russian cooperation in biological science and technology has increased significantly. Cooperative programs provide many opportunities to apply strong Russian scientific capabilities to activities that benefit both Russia and its partners. Yet the existing U.S. programs, which address biological issues in Russia, continually face political, scientific, and financial difficulties that jeopardize their long-term sustainability. An important theme of this report is the significance of expanding cooperation in ways that overcome and eventually reduce such impediments.

In addition to the United States, other countries have also joined with Russia in combating infectious diseases. These bilateral and multilateral efforts indicate that the international community clearly recognizes the profound global implications of biology-related developments in Russia. These programs have also had a significant effect on Russia's approach to these issues as well. Within the context of Russian participation in Western initiatives over the past decade, the Russian government's vision for the nation's future in public health and related fields has evolved. Policies designed to realize that vision are significantly influenced by approaches advocated by western partners and demonstrated through programs funded internationally.

In addition to a vision for the future, the Russian government has developed a conceptual framework for strengthening the public health system of the country on a continuing basis. Relevant ministries are also well aware of the need to develop more coherent policies and programs for combating agricultural diseases, for promoting research and development, and for supporting the emergence of biotechnology firms. But implementation of such efforts is severely constrained financially, therefore international support will continue to be important.

Against this background, in 2003, a committee of the National Research Council (NRC), building on a decade of promoting U.S.-Russian engagement in biological research, initiated this study to be conducted in close consultation with Russian colleagues. The objective was to set forth a realistic vision for the development of the biosciences and biotechnology in Russia over the next ten years. The committee was to consider practical steps that could be taken independently by Russia, or collaboratively with international partners, to move toward achievement of that vision. The Nuclear Threat Initiative, a private foundation, and the NRC provided financial support for the study.

This report presents the findings and recommendations of the committee developed over the course of the multi-year study. It addresses both contributions to peaceful scientific, economic, and social development of Russia's biology-oriented institutions and the prevention of the misdirection of materials and expertise to terrorist groups or to states seeking biological weapons capabilities. In general, a strong public health system, coupled with an active research base and a commercially viable biotechnology sector, can contribute to the achievement of both goals. The development of an infrastructure to help control infectious diseases and the potential contributions of international cooperation to support such an infrastructure are the focal points of this report.

The specific charge to the NRC committee responsible for this study was as follows:

> This project will present a 5 to 10 year vision of an environment in Russia for biological research and production activities that encourages efforts to prevent bioterrorism and the proliferation of potentially dangerous biological agents and expertise while addressing relevant public health, agricultural, industrial, environmental, and scientific challenges. The project will address both: (1) the

> positive contributions to peaceful scientific, economic, and social development that can be made by biological institutions; and (2) the possibilities of misdirection of materials and expertise to terrorist groups or to states seeking biological weapons capabilities. Also, the project will suggest near-term steps that can be taken by the Russian government, by Russian institutions, and by the international community to contribute to the development of such an environment. U.S.-Russian cooperative programs will receive special attention, since during the past several years they have played a key role in reducing the likelihood of bioleakage (the spread of biological materials and expertise) from Russian institutions.

The committee recognizes that the recommendations set forth in this report will be meaningful only if they are embraced by Russian officials and specialists as well as by American and other international counterparts. Therefore, the report draws on extensive interactions between committee members and Russian colleagues over the course of 18 months in an effort to ensure that the recommendations are realistic, with a reasonable chance of broad acceptance in Russia. At the same time, the committee has been sensitive to the interests of Russia's partners, especially U.S. government departments and agencies. The committee believes that these partners will be receptive to many of the recommendations presented in the report.

As indicated in Appendix B, committee members and staff visited more than 30 relevant government organizations, research centers, commercial firms, and educational institutions in Russia and consulted with more than 100 knowledgeable Russian officials and specialists during the course of the study. In addition, they attended three conferences in Russia on topics addressed during the study, and they invited leading Russian specialists to participate in a special meeting on the themes of the study in the United States. Similarly, dozens of American and European officials, specialists, and interested observers who are familiar with Russian policies, activities, and attitudes were consulted. Thus, the recommendations set forth in this report are well grounded in authoritative views on the conditions, developments, and trends in Russia. Russian government bodies, international organizations, foreign aid agencies, and other Western organizations operating in Russia have issued related reports on trends, expectations, and limitations in biological science and technology. Several of the most important publications are cited in this report. However, for many of the issues discussed in the report, limited or no written documentation was available to the committee. Therefore, the judgments of the committee were based in large measure on the discussions and personal observations of committee members and staff.

For well-informed Russian colleagues, there may be little information and few ideas that are new in this report. Many of them have argued for years that a principal problem facing almost all Russian organizations is the lack of funds for salaries, equipment, start-up capital for commercial ventures, and operating expenses. The committee is optimistic, however, that even for our best-informed colleagues in Russia, the report will help focus discussions and decisions on policies and programs with the highest payoff—now and in the future—in a country that is still recovering from the enormous economic shocks of the past decade.

While funds are obviously important, Russian colleagues are also aware of the importance of appropriate policies, priorities, and incentives for combating infectious diseases. As an example of the intentions of the Russian government, Government Decree #1187-r of August 21, 2003, set forth a plan for the stimulation of innovation and the support of venture capital investments.[1] The plan covers the creation of governmental support mechanisms for conducting major projects aimed at: (1) creating competitive, science-intensive products; (2) developing systems for sharing scientific and technical information; (3) improving conditions for production of high-tech products; and (4) reducing commercial risks for innovative activities. However, securing sufficient funding to provide a stimulus in these areas has, and may well continue to be, a challenge into the future.

Rather than repeat the efforts of others, or attempt to address all aspects of biological science and technology, the committee decided to focus on a few key dimensions of Russia's biological research, production, and service infrastructure about which it can make well-founded judgments. Indeed, it simply would not have been possible within the time and financial constraints of this study to cover all aspects of these fields. Thus, as suggested earlier, this report concentrates on disease agents, particularly those that could pose a threat to large population groups, whether introduced through natural or terrorist means.

The committee did not attempt to address the biological capabilities and related activities of the Russian Ministry of Defense. The ministry's activities in biological research and development are believed to be significant, and they should be oriented not only toward supporting narrowly defined military missions but also to reinforcing broader public health efforts. But the committee simply did not have sufficient authoritative information to make judgments on the policies, programs, or future role of Russian military and military-related organizations. The committee did consider the activities at some institutions that were once involved in Soviet military activities, especially the institutes affiliated with Biopreparat, since committee members had considerable experience in interacting with these organizations (see Box 4.1).

In addition, the committee did not consider issues associated with international negotiations to strengthen the Biological Weapons Convention, even though these negotiations have implications for international scientific cooperation. The committee believed that an analysis of the process of international negotiations

[1]The reference to this decree was provided to the committee by a senior Russian researcher in October 2004. The decree outlines a plan for the stimulation of innovation and support of venture capital investment.

would have detracted from fulfilling its primary charge and therefore decided to concentrate on other aspects of Russia's future in bioscience and technology.

As previously noted, a recurrent theme throughout the report is the need for additional funding. There are a number of funding sources for health-related and agriculture-related activities in Russia, in particular Russian ministries and agencies, foreign governments, and international organizations. The committee considered the possibility of developing a conceptual framework for evaluating the relative importance of approaches that are recommended in this report. However, each funding source has its own priorities and criteria, therefore such a framework would be of little use. At the same time, the committee has been mindful of the need for more detailed analyses of the costs and benefits of each recommendation, and such analyses should be undertaken by the responsible Russian organizations that have access to more detailed and more authoritative information concerning costs. Nevertheless, the committee considered the funding capabilities of relevant organizations when developing its recommendations. Of particular significance will be the interest of senior Russian government officials in the recommendations, since they must make policy judgments concerning the allocation of resources.

Slow Recovery of Russian Capabilities in Biological Science and Technology

Russia has a vast array of biological research and development facilities staffed by tens of thousands of scientists, engineers, and technicians who are capable of contributing in many ways to public health, agricultural, and industrial activities. Russia's ecological diversity and expanse are unparalleled, and its specialists have a long and distinguished history in research and epidemiological investigations of many infectious agents of global interest. They have developed valuable banks of biological specimens and scientific data, including materials and information from remote areas of Russia and nearby countries where outbreaks of disease are of continuing concern. Clearly, significant portions of Russia's technical strength have declined in recent years, but the nation's remaining biological expertise is still of considerable importance.

The early years of this millennium find Russia slowly recovering from the financial difficulties of the 1990s. Economic challenges have engendered worldwide concern that Russia may have inadequately controlled biological assets, including organisms in storage areas and laboratories, in addition to the well-known specialized knowledge of many researchers. Dangerous strains and relevant technologies could be tempting targets for nefarious parties determined to misuse advances in biology to destroy their adversaries.

Fortunately, the political and economic trends that affect health and agriculture identified below are generally favorable. Therefore, achieving the ten-year vision for Russia set forth in Chapter 2 is much closer to reality than it would have been just two or three years ago.

- Both politicians and the general public recognize the dire consequences of the deterioration of the health of the population in Russia. Unproductive workers, unfit military conscripts, debilitated pensioners, and underachieving children are causing increasing public demands for greater allocations of government resources to the prevention and treatment of widespread health problems. These problems include HIV/AIDS, tuberculosis, hepatitis, influenza, measles, and nosocomial infections that affect large segments of the population.[2]
- Russian investments in health-related research programs are increasing, and Russian research institutions are successfully competing for external resources. This allows research institutes greater control in determining their research agendas. They are no longer tied directly to the priorities of foreign organizations which were once the primary funding source for many institutes.
- As Russia's economy improves, its embryonic biotechnology industry is charting an ever more optimistic course and is beginning to achieve success. Many Russian entrepreneurs understand what is needed to compete effectively in an evolving market economy, both in concept and in practice. They are also devising approaches to overcome the difficulties of marketing products domestically and internationally in both the agricultural and public health arenas. Although Russian investors are often hesitant to risk their funds in biotechnology endeavors, a few—particularly those backed in part by government financing—have begun to take risks.
- Sensitivities within the Russian government regarding the dangers of bioterrorism and a recognition of the steps needed to reduce this threat are increasing (see Box I.1). Of particular concern is the possible misuse of infectious agents that cause anthrax, plague, and smallpox. Extremists or mercenaries with ties to Chechen separatists seem to be of the greatest concern in this regard within Russia.

Despite these advances, the recovery period from the economic collapse of the 1990s will be long, and the emergence of demands from paying customers for biotechnology products will be delayed accordingly. Government resources for enhancing health care at the regional and local levels in Russia will undoubtedly remain modest for many years to come. All the while, skepticism will continue to mount in Russia about the quality and effectiveness of imported drugs from developing countries, even though such imports may be omnipresent on Russian store shelves.

Nevertheless, discernible progress in combating infectious diseases can be made if political will and available resources are carefully directed at the priority topics suggested in this report. The Russian government must, of course, continue to develop its own vision of the future, and this report should provide useful

[2]The dire state of the public health care system in Russia is discussed in C. Dye, 2005.

BOX I.1
A Russian Perspective on the Bioterrorism Threat

"Realization of the threat by government agencies is deepening, but it is still in the embryonic stage and not manifested in tangible counter-measures. The growing concern is a consequence of the concern on the part of experts who have been vocal in communicating their views."

SOURCE: Russian biological scientist (November 2004).

ideas to that end. Yet neither the Russian government nor the international community will be able, in the near term, to finance all of the additional activities that are needed. Therefore, necessary activities should be supported incrementally, beginning as soon as possible.

It is essential when setting priorities, however, that the Russian leadership establish a comprehensive framework for addressing all aspects of combating infectious disease. Recent events in Russia indicate progress in this regard. In 1997 the Duma passed a law requiring the development of a concept for improving the public health and the medical science situation (see Appendix C). Since that time various government ministries have been developing goals and objectives for policies and programs that carry out that concept (see Appendix D for an example of this effort). This report provides additional ideas and recommendations that should be helpful in further efforts to transform that concept into practical results, which benefit the population of Russia and contribute to global health more broadly.

Throughout the course of this study, the organizational structure of the Russian government underwent substantial changes (see, for example, Box I.2 on new, high-level organizational responsibilities for health-related activities and Appendix E for the responsibilities of the new Federal Service for Supervision in the Sphere of Health and Social Development). While a reformed array of ministries, agencies, and committees took shape during 2004, the new Ministry of Education and Science almost immediately proposed a reconfiguration of the hundreds of public research institutions that are active in all areas of science, particularly those affiliated with the academies of sciences of the country. As this report went to press, the debate over whether and how to reduce the number of research institutions was under way. While this report discusses the need to concentrate limited resources at selected centers of excellence, there has been no effort to analyze alternative configurations of Russia's research complex.

BOX I.2
Organizational Structure for Health Activities in Russia

Ministry of Health and Social Development

- Federal Agency for Health and Social Development
- Federal Medical-Biological Agency
- Federal Service for Surveillance of Consumer Rights Protection and Social Welfare
- Federal Service for Surveillance of Health and Social Development

SOURCE: Ministry of Health and Social Development (May 2005).

U.S. Interest in Cooperation

The U.S. interest in bilateral cooperation with Russia in the fields of biological science and technology has been stimulated in part by the following factors:

- high potential of Russia's biological research and industrial complex to support both civilian and military programs
- significance of efforts by the Russian government during the past several years to revitalize research capabilities and apply them to solving social and economic problems
- Russia's vast ecological diversity, which offers unique environments for research in the life sciences and provides opportunities for detecting the early emergence and movement of dangerous diseases of global importance
- marketing opportunities within Russia for western companies that provide biological products and services

Many of the cooperative activities promoted by the U.S. government during the past decade have been nonproliferation programs designed to help prevent the spread of Russian expertise to countries and groups that may attempt to develop biological capabilities for purposes hostile to U.S. interests. Directly related cooperative programs supported by the U.S. government are aimed at improving the security of biological strains and related materials within Russian facilities in an effort to prevent their acquisition by unauthorized persons with nefarious intentions. Thus, U.S. government-sponsored programs have involved a variety of research groups in Russia that include many scientists who had participated either directly or indirectly in the Soviet biological weapons program. The principal bilateral programs are described in the text and appendixes of this report.

Smaller cooperative programs—financed by the U.S. government and by

U.S.-based private foundations—have supported the exchange of individual scientists and the development of collaborative research projects not limited to former Russian military-oriented specialists.

In the commercial sector, a few U.S. companies have supported biological research projects and manufacturing of biological products in Russia, sometimes with U.S. government assistance. However, most Western biology-oriented companies have limited their investments in Russia. The financial risks are often too great despite the high qualifications of potential Russian partners. They have preferred to seek quick sales of a few products while waiting to see how the environment for broader business ventures in Russia develops. A few international companies are developing major efforts to sell vaccines, drugs, and diagnostic products that have been produced abroad in Russia. Several have shown interest in establishing their own production facilities in Russia when there are financial incentives, particularly through foreign assistance programs.

In sum, most cooperative efforts have been in the scientific arena rather than the commercial arena. The positive influence of cooperative programs, both public and private, in sustaining Russian research efforts during a time of economic deprivation should not be underestimated.

Background Provided by Related NRC Reports and Consultations in Russia

During the past decade, the Institute of Medicine, with support from a variety of U.S. government organizations and private foundations, has published numerous reports that address microbial threats to populations worldwide, highlight new concerns over bioterrorism, and review the adequacy of U.S. laws and regulations in the control of dangerous pathogens. For example, the 1992 report *Emerging Infections: Microbial Threats to Health in the United States* warned leaders in the United States and abroad that infectious diseases are becoming an increasing security threat. The 1997 report *America's Vital Interest in Global Health* underscored the significance of the spread of infectious diseases across boundaries at accelerating rates. The 2003 report *Microbial Threats to Health* highlighted the connections between biological, environmental, social, and political factors that complicate the development of meaningful and sustainable solutions to address infectious diseases. The related report, *Countering Agricultural Bioterrorism,* undertaken by the NRC's Board on Agriculture at the request of the U.S. Department of Agriculture, also provided helpful background for conducting this study (see Appendix F for a list of recent reports about developments in global health published by the National Academies).

In 1997, the National Academies released *Controlling Dangerous Pathogens, A Blueprint for U.S.-Russian Cooperation.* This report, financed by the U.S. Department of Defense (DOD), provided an important framework for new cooperative activities. It emphasized the benefits to both countries—particularly the scientific, public health, security, and political benefits—of an expanded bilateral engagement program involving Russian institutions that had been engaged in biodefense activities during the Soviet era.

Since that time, the NRC has sent several scientific teams to Russia to conduct peer reviews of Russian research proposals that were considered within the framework of DOD's nonproliferation efforts funded by the Cooperative Threat Reduction program (also known as the Nunn-Lugar program). Additional recent visits to Russian institutes by members of this committee have been supplemented by a wide range of consultations with U.S. and Russian policy officials and entrepreneurs about developments in Russia well beyond defense-related activities and have provided further insights that are incorporated into this report.

This report expands the focus of the 1997 National Academies report *Controlling Dangerous Pathogens*. While the earlier report concentrated on bilateral programs of potential interest to DOD, this report places the issues in a much broader global context and emphasizes steps that should be undertaken by both the Russian government and international partners. The economic conditions, the priorities attached to public health issues, and the concerns over bioterrorism in Russia have changed dramatically since 1997. Moreover, the size and scope of U.S.-Russian collaborative efforts have expanded greatly in recent years. Still, like the 1997 report, this effort should be useful to those officials and specialists in the two countries who are developing plans for future U.S.-Russian cooperation in preventing, detecting, or controlling the ever-present danger of infectious disease outbreaks whether they are naturally occurring or intentionally introduced. As other countries expand their interest in cooperating with Russia, the lessons that have been learned in the course of this study should be helpful to them.

ORGANIZATION OF THE REPORT

Chapter 1 presents a brief review of the context for U.S.-Russian cooperation in addressing the threats of infectious diseases that lie ahead. It sets forth important aspects of a vision for Russia's development of biological science and biotechnology over the next 10 years and briefly describes the current state of Russian policies and programs in this field.

Chapters 2 through 5 discuss four topics that are of central importance to the evolution of a stronger research and technology infrastructure in Russia. They are as follows:

- strengthening Russia's surveillance capabilities for detecting, diagnosing, and reporting outbreaks of both well-known and newly-emerging diseases (Chapter 2)
- focusing laboratory research and epidemiology to support priority public health programs and related agricultural programs more effectively (Chapter 3)
- developing a high-quality biotechnology sector that in time will reduce

dependence on imports of foreign vaccines and drugs while providing improved and affordable support to the health and agriculture sectors (Chapter 4)

- nurturing a new generation of young Russian leaders in biological science and technology (Chapter 5)

Progress in each of these areas can improve the basis for achieving a vibrant and sustainable capacity to address both the immediate and the long-term social, economic, and security needs of Russia that are intertwined with biological science and technology. Such progress can also provide new opportunities for international engagement that benefits the global community more directly.

Chapter 6 of this report highlights several cross-cutting issues directly related to expanded and more effective U.S.-Russian cooperative activities. It calls for a new high-level intergovernmental commission to promote cooperation. A further significant goal is the continued integration of former defense facilities and associated technical personnel into the broader civilian scientific infrastructure of the country. Sources of financing to sustain programs that help prevent the emergence and reemergence of infectious diseases are also important. New funding sources can reduce obstacles to international cooperation while encouraging a true partnership between the scientific communities of Russia and the United States.

Finally, a number of figures, tables, boxes, and appendixes provide supplemental information and perspectives on recent developments in Russia. The committee does not endorse these documents and comments nor the accuracy of the data presented, but the committee believes that they contribute to the context for the report.

1

A Vision for Russia's Future

A concerted global effort is needed to combat naturally occurring and intentionally introduced infectious diseases that can cause severe illnesses, disability, and death. In recent years, West Nile encephalitis, severe acute respiratory syndrome (SARS), monkey pox, and avian influenza have been but the latest diseases that have dramatically raised U.S. and international concerns over the need to strengthen both early warning and response systems throughout the world. At the same time, criminal elements have contaminated the U.S. postal system with anthrax spores, underscoring the reality of bioterrorism. Thus, we cannot delay in taking bold steps to minimize the threats from pathogenic microbes and ensure that these resilient, dangerous foes do not overwhelm public health systems, disrupt food supplies, devastate economies, or create uncontrollable anxieties among populations.

Russia, with its vast ecological diversity and a large, well-trained scientific workforce, should be a leader in efforts to prevent, detect, and respond to the emergence and resurgence of infectious diseases, at home and abroad.

In addition to the aforementioned threats, many other infectious agents pose serious problems in Russia. The rapid growth in HIV/AIDS cases in Russia is of worldwide concern and could have a devastating effect on the population (see Box 1.1). Tuberculosis has also spread rapidly in recent years. Hepatitis A, B, and C and cholera challenge health authorities, and tick-borne encephalitis and other tick-borne diseases have changed the Russian tradition of walking in the forests. Influenza, chicken pox, and scarlet fever have had a negative economic effect in Russia. Plague, tularemia, and hemorrhagic fever are also frequently encountered. In the agriculture sector, brucellosis, rabies, and foot-and-mouth disease

BOX 1.1
HIV/AIDS Epidemic in Russia

An estimated 860,000 people were living with HIV in Russia at the end of 2003, fully 80 percent of them were between15-29 years of age and more than one-third of them were women. HIV prevalence is increasing steadily. Infection levels among pregnant women have risen from less than .01 percent in 1998 to .11 percent in 2003. At the heart of the country's epidemic are the extraordinarily large numbers of young people who inject drugs and have active sex lives. In early 2004, more than 80 percent of all officially reported HIV cases were drug injectors.

SOURCE: AIDS Epidemic Update, UNAIDS, and WHO (December 2004).

are too often found on Russian farms (Onishchenko, 2002; Pokroksky, 2002: 5; WHO, 2003).

RUSSIA'S UNIQUE CHARACTERISTICS

Although the public health situation in Russia is clearly similar to that in other industrialized nations, Russia faces several unique challenges in safeguarding public health and protecting its agriculture. The physical environment of Russia, in which diseases emerge and spread, geographically stretches across 12 time zones and 4 ecological zones, producing infectious agents that vary widely in type, frequency of occurrence, and persistence. Russia has densely populated industrial regions with well-established public health infrastructures, manufacturing centers in sparsely populated areas with limited support services, and vast agricultural regions. This diversity complicates the government's ability to provide adequate protection from outbreaks of diseases across different regional settings.

Second, as Russia evolves from being a centrally managed but relatively prosperous nation to having a free market economy, social and economic upheavals continue to cause problems. Disruptions in living patterns and in the availability of health services have increased the susceptibility of large segments of the population to disease. Additionally, the sharp erosion of the technological base for the manufacture of drugs, vaccines, and medical devices has opened the door for a large influx of foreign products that now inhibit the recovery of a Russian pharmaceutical industry capable of producing cheaper and better products.

In recent years, the budget of the former Ministry of Health (now incorporated into the Ministry of Health and Social Development) has been slowly growing (see Figure 1.1), but it is still small relative to the needs of the population.

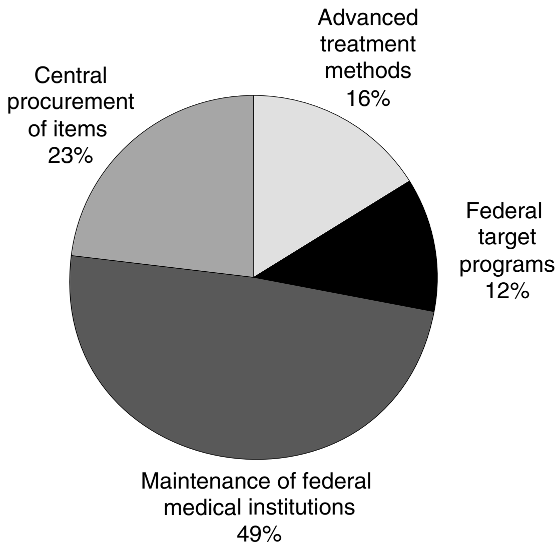

FIGURE 1.1 Allocation of federal budget to support Ministry of Health and Social Development, Russia. SOURCE: Ministry of Health and Social Development, 2004b.

Further, responses to concerns over bioterrorism are placing additional strains on the budget. Appendix G describes the strategy of health officials to combat bioterrorism, and Appendix H presents a broader Russian view of responses needed to address that threat.

GOALS FOR CONTROLLING INFECTIOUS DISEASES

Despite these difficulties, a realistic, ten-year goal for Russia is the evolution of a stronger, more flexible public health system that is increasingly integrated into the global community. This evolution will continue even as Russia responds to endemic and emerging diseases, including zoonotic diseases. For example, an enhanced public health system could contribute to more effective utilization of disease prevention measures and more effective control of arthropod vectors and animal populations that serve as reservoirs for human diseases. In time this should result in a significant reduction of vaccine-preventable and drug-curable infections in both humans and animals across Russia. On a broader scale, Russian achievements would make greater contributions to a more effective global approach to combating infectious diseases as improved and enhanced international cooperation develops.

To achieve this goal of a more robust public health system, the committee recommends strengthening Russian policies and programs by:

- focusing on surveillance, laboratory diagnostics, and the development of counter-measures (e.g., drugs, vaccines) capable of addressing diseases in the broadest sense
- improving capabilities to detect and diagnose new, reemerging, and antibiotic-resistant pathogens in both rural and urban settings and upgrading communication systems to provide timely and accurate information
- enhancing disease surveillance, encompassing affected species of significance
- monitoring food and water supplies for safety and potability
- supporting well-focused research projects that strengthen the base of fundamental scientific knowledge
- strengthening programs to facilitate the commercialization of scientific findings within a regulatory framework that supports public health and the protection of agriculture
- developing an improved understanding of the relationships between infectious agents and important chronic diseases, a priority of growing international interest
- supporting the emergence of a strong biotechnology sector that enhances efforts to combat infectious diseases affecting the Russian population
- developing and implementing effective security procedures at the hundreds of facilities that can propagate, store, or distribute pathogens that, if diverted, could be used for bioterrorism; an important initial step is to conduct a careful nation-wide inventory of the many collections in Russia and consolidate collections where appropriate
- promoting broad transparency of Russian research and health-prevention and control activities involving dangerous pathogens in order to reduce international apprehensions regarding the possible misuse of Russian research or unauthorized diversion of infectious agents, with comparable transparency also expected in other countries
- recruiting, training, and retaining an expanded cadre of biomedical scientists, medical doctors, veterinarians, plant pathologists, epidemiologists, and other relevant specialists who are equipped with modern technology and positioned to deal with infectious disease threats.

As noted before, Russia has well-established institutions that are needed to support the achievement of these objectives. Even though many relevant scientific and operational capabilities have declined over the past decade, some institutions have maintained their long-standing ability to protect the health of the Russian population. The structure into which their institutes are integrated is described below; it is the point of departure in responding to both current and future challenges.

- The Ministry of Health and Social Development, Ministry of Agriculture, Ministry of Education and Science, Ministry of Economy, several other government bodies, and the State Duma develop government strategies, policies, and funding priorities for health-related and agriculture-related research programs. They also develop regulatory and inspection requirements, and promote the science and business environments in Russia.
- A nationwide network of 2,300 State Sanitary Epidemiological Surveillance Centers monitors and reports disease trends and outbreaks. These centers, which have been under the direction of a special organization within the framework of the Ministry of Health and Social Development and its predecessors for many decades, are designed to provide a unified approach to monitoring and reporting.
- Numerous agricultural institutes and related stations under the purview of the Ministry of Agriculture and the Academy of Agricultural Sciences monitor animal and crop diseases. They, too, should provide a unified approach to monitoring and reporting.
- Numerous public sector research units that employ tens of thousands of scientists dedicated to fundamental and applied research are relevant to combating human and agricultural diseases. They are dispersed across various government bodies, within the frameworks of academies of sciences, and at centers associated with higher education institutions.
- The Pharmaceutical Committee approves all drugs, vaccines, and other medical products for human use that are domestically produced or imported into Russia. An analogous committee approves agricultural products.
- Laws have been enacted and dozens of committees have been established to address the biosafety aspects of genetically modifed organisms. Profitable commercial activities have not yet emerged, however.
- Newly enacted laws provide the Russian Patent Agency with new authority to protect intellectual property as the court system begins to handle patent infringement cases.
- Dozens of university-level educational institutions are dedicated to training specialists in medicine, biology, epidemiology, veterinary sciences, plant sciences, and other fields important for controlling infectious diseases.

Despite the existence of this complex structure, almost all of the above-mentioned institutions urgently require enhanced capabilities. New laws and regulations need further development and more effective enforcement. Even though the outstanding achievements of Russian leaders and specialists in bioscience and biotechnology are numerous, many institutions suffer not only from

BOX 1.2
Weak Protection of Intellectual Property

"In Russia, copyright protection virtually does not work. In rare instances when researchers receive a worthwhile reward for a new drug, it is not a result of a legal mandate or requirement. It is the result of a personal agreement (not legally documented in any way) with the manager (owner) of the manufacturing company or as a result of the inventor's leverage to control the production flow (in particular, when the inventor can terminate the production at his own volition)."

SOURCE: Russian bioresearch manager (November 2004).

financial difficulties but also from a legacy of favoritism and excessive central control that inhibit initiative and effectiveness. Some have serious shortages of qualified and motivated personnel. Others have shifted their attention from serving the needs of the public to the search for immediate commercial success. Still others have taken shortcuts, fulfilling their obligatory commitments in less than an adequate manner.

Many additional challenges remain. Much of the laboratory equipment for disease surveillance and related research is now obsolete. Russian specialists have been forced to become remarkably skilled in making the best of antiquated equipment. Enforcement of regulatory requirements covering the development and distribution of health-related products is often inconsistent. Sometimes enforcement is excessive, and sometimes it is non-existent. New intellectual property laws are only now being tested in the Russian courts and are frequently ignored (see Box 1.2). The Russian biotechnology industry is in its earliest stages of development, and few investors are prepared to enter an arena plagued with corruption, bureaucratic delays, and other obstacles. Finally, because of the depressed job market for scientists, only a low percentage of university biology graduates (less than one-third at some institutions) pursue scientific careers.

The remainder of this report suggests specific steps that can be taken by Russia, with support from international partners, to help transform the vision of today into the reality of tomorrow.

2

Pillar One: Improving Surveillance and Response

Successful disease control measures are based on effective integration of human and animal disease surveillance and response programs. Examples of essential routine surveillance and response activities are: (1) identifying and tracing contaminated food and issuing warnings and recalls; (2) diagnosing prevalent influenza virus strains to guide vaccine development and use; (3) monitoring the blood supply to ensure its safety; and (4) tracking the spread of antibiotic-resistant infections and instituting controls as necessary. To heighten the likelihood of containing infectious diseases through effective surveillance and response, whether the diseases are common infections or newly emerging threats, a nation needs support from all levels of government and cooperation among health care and veterinary networks throughout the country (CDC, 1998a, 1998b).

In brief, surveillance begins with systematic collection, analysis, and dissemination of data related to the health of the population, including animal diseases that could be transmitted to people. Important data include information on clinical diagnoses, laboratory-based test results, specific syndromes, health-related behaviors, and those related to the use of products to combat diseases such as the sales of antimicrobial drugs. These data provide the basis for detecting outbreaks, characterizing disease transmission patterns, developing prevention and control alternatives, and conducting evaluations.

Enhancing surveillance capabilities to provide better, timelier, and more informative data is a never-ending process. Many countries are currently concentrating on: (1) integrating public health information banks and surveillance data systems, and more effectively utilizing data available in the broader health community; (2) applying molecular fingerprinting, ranging from the identification of strains of *E. coli* and *Salmonella* to tracking the spread of HIV/AIDS and brucellosis, for example; and (3) identifying the presence of those microbes and viruses of particular bioterrorism concern (CDC, 1998a, 1998b).

Responding to warning signals from surveillance activities is also essential for protecting the population. The response may be limited to confirming initial reports and then ensuring that authorities are taking appropriate control measures, or it may entail a broad international response to threats that cross national borders. A response may require special localized surveillance and control efforts or wider-scale efforts as the likelihood of disease proliferation becomes clear. Additionally, it may depend on a country's surge capacity to quickly deploy resources without interrupting routine activities. Finally, surveillance responses will probably generate considerable scientific information that may be useful for addressing similar problems in the future.

IMPORTANCE OF SURVEILLANCE AND RESPONSE IN RUSSIA

The Russian Ministry of Health and Social Development devotes much of its attention to socially significant diseases (see Appendix E). It receives frequent reminders of their importance, such as the nationwide outbreak of diphtheria in 1993-1996; the emergence of polio in Chechnya in 1995; the surging incidence nationwide of tuberculosis, syphilis, and hepatitis B; and even continuing malaria infections in some localities. At the top of the list of the newer diseases of concern are HIV, followed by hemorrhagic fever, Lyme disease, and 25 other potentially dangerous infections (Onishchenko, 2002). These realities force health authorities to improve preventive measures to combat common infectious diseases, generally within the framework of national immunization strategies and policies (see Appendix I).

The Russian government has not hesitated to respond promptly and vigorously, within the constraints of available specialists and funds, to disease threats once they have been identified. As an example of Russian capabilities, the government response to the severe acute respiratory syndrome (SARS) outbreak in China was impressive. Attendants on Russian passenger trains leaving China and personnel at Russia's international airports were important components of this response. These personnel, who had been routinely trained to cope with sick travelers, were quickly given supplemental information to enable them to identify travelers who might be infected with SARS. Those travelers then had immediate access to public health personnel for professional health examinations when needed. Despite the long Russia-China border, SARS did not infect the Russian population with the possible exception of one questionable case in the Far East.

The government is also organized to respond to an incident of bioterrorism, particularly in Moscow, which is considered by many Russians the most likely target of such an attack. Special medical manuals have been prepared. Special organizations have been designated to provide the needed health-related technical support to the Ministry for Emergency Situations, which coordinates all responses in cooperation with city authorities. Emergency assignments have been made to units of the Ministry of Health and Social Development. However, Russian officials readily admit that in recent years there has been a considerable degradation in their ability to detect or respond to disease outbreaks, including bioterrorism incidents outside Moscow and St. Petersburg.[1]

Unfortunately, in Russia the initial detection and assessment of a naturally occurring or human induced outbreak is hampered by several factors. They include inadequate diagnostic capabilities, outmoded communication networks across vast geographic areas that might be part of infected zones, and the reluctance of ill people to turn to a Russian health system that had previously provided services free of charge but now may require payment for services of adequate quality. Any degradation of capabilities is of concern to the Ministry of Health and Social Development and related agencies. Therefore efforts are under way to correct deficiencies that have arisen since 1991.

The Russian Ministry of Agriculture has long been concerned about the prevalence of common diseases, such as foot-and-mouth disease, rabies, brucellosis, and wheat rust. It devotes considerable effort to monitoring for these and other diseases. More than 200 research institutes associated with the ministry and the Academy of Agricultural Sciences are located throughout the country (see Appendix J). Many have a role in monitoring and reporting animal and plant diseases. The ministry and the academy justify the need for the large number of research institutes by pointing to the country's size and its many different agroecological regions and diseases. The Veterinary Service of the Ministry of Agriculture also monitors the condition of a limited number of animals, particularly if there are reports of outbreaks from farmers or other sources. Finally, the anti-plague institutes, discussed later in this chapter, provide a front line for surveillance. Specialists at these institutes routinely collect and analyze rodents and other potential reservoirs of animal and human diseases.

Much like the decline in capabilities in human health surveillance and response, Russia's capability to detect and diagnose agricultural problems has eroded in recent years. The incentives to expend resources on animal or plant protection are not great, and the lack of priority they command obviously has implications for human health.

Another area of concern to public health and agricultural officials is the integration of the systems for detecting food-borne diseases with food monitoring systems. A useful step suggested by a Western expert would be to use *Salmonella*

[1]See for example, Interactions Among Government Agencies, Institutions, and Specialized Bodies for Liquidation of the Consequences of Terrorist Acts Involving Pathogenic Biological Agents and Dangerous Chemical Substances, Methodological Recommendations, MP0100/3556-04-34, State Sanitary Epidemiological Standards of the Russian Federation, Moscow, 2005.

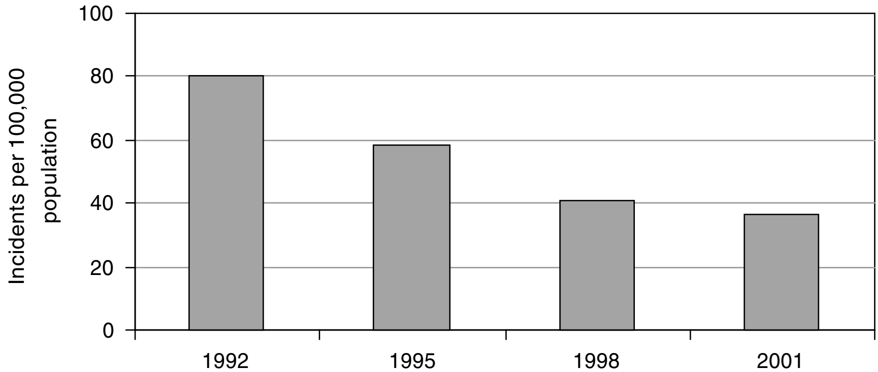

FIGURE 2.1 *Salmonella* incidence in Russia, selected years, 1992-2001. SOURCE: Onishchenko, 2002: 26.

as a case study.[2] Through applying lessons learned from investigations of outbreaks of *Salmonella,* the two types of monitoring systems might be brought closer together. Since the World Health Organization (WHO) has established a collaborating center on *Salmonella* at the Central Research Institute of Epidemiology in Moscow, such an initiative would probably be easy to implement. As indicated in Figure 2.1, *Salmonella* outbreaks are on the decline in Russia, but they remain a public health concern and provide a good topic for detailed examination.

SURVEILLANCE AND MONITORING SYSTEMS

System of State Sanitary Epidemiological Surveillance Centers (SSESCs)

A system for combating and controlling infectious human diseases, unique in both size and standardization of approach, has been functioning in Russia for many years. The State Sanitary Epidemiological Service has 89 regional centers and 1,700 district-level centers. Overall, the system covers the entire country with about 2,300 centers, and employs over 6,000 medical doctors and many other specialists. In addition to carrying out critical surveillance and response functions, these centers are important in developing research priorities such as the following recent examples (Onishchenko et al., 2003):

- new rapid pathogen detection diagnostics and tools based on cutting-edge research in the field of biotechnology and nanotechnology

[2]Suggestion of senior American agricultural official stationed in Moscow.

- next generation vaccines and live recombinant vaccines based on viral vectors developed through genetic engineering methods
- new chemical substances and formulations for disinfectant agents

Unfortunately, since the disintegration of the Soviet Union, the system has lost some of its capabilities, despite the ever-increasing variety of infectious diseases in Russia. The sanitary epidemiological center that serves the city of Moscow has state-of-the-art capabilities to identify, diagnose, report, and analyze data. However, many SSESCs in the outlying areas of the country have had difficulty paying employees, let alone replacing outmoded analytical equipment and installing modern communications equipment. Although the health sector receives generally favorable consideration in the federal budget process in Russia, the competing internal demands for increased government resources are severe. The continued economic recovery should improve prospects for increases in government funding for health and agriculture surveillance, but many of the facilities are currently facing financial difficulties.

The Anti-plague Surveillance and Research Network

The Russian anti-plague network includes 5 institutes and 12 stations that operate throughout Russia (see Appendix J). The institutes address a number of diseases in addition to plague, including, for example, anthrax and tularemia. These institutes have regional orientations, concentrating on infectious agents of particular concern to those regions. The stations similarly concentrate on local problems as would be expected.

During the Soviet era, this network of facilities was important in addressing disease outbreaks not only in Russia but also in other Soviet republics. Although the Russian components of the former network now concentrate primarily on problems in Russia, they still play a role as a technical resource for supporting activities organized by the governments of neighboring countries in Central Asia and the Caucasus. One institute, the Stavropol Scientific Research Anti-plague Institute, has served as a WHO collaborating center since 1973, and has sent teams to China and Mongolia; but it has had only limited interactions with Western institutions (Stavropol Scientific Research Anti-plague Institute, 2003).

IMPROVING SURVEILLANCE AND RESPONSE

Set forth below are two structural and organizational recommendations that could contribute to the improvement of Russia's surveillance capabilities. These initiatives are intended to help: (1) determine the incidence and prevalence of endemic and emerging infectious agents in humans and animals; and (2) improve the detection, diagnosis, and identification of infectious agents within a national reference laboratory system that is connected to the global system of the WHO. If

Russia builds on its long history of successful epidemiology and disease surveillance, it will be in a position to develop strong state-of-the-art abilities to investigate disease outbreaks. The following suggestions are modest in scope, but nevertheless can spotlight important practical steps that should be taken on a broader basis.

A realistic approach to strengthening Russian capabilities for disease surveillance and response over the next ten years is to make incremental improvements throughout the SSESC system. **To guide this effort, the committee recommends prompt establishment of two model SSESCs for surveillance, diagnosis, analysis, and communication of information concerning infectious disease episodes.**

One center would be at the regional (oblast) level and a related center would be at the local level within the same region. Geographical integration of the two centers would provide many opportunities to demonstrate how communications and cooperation within and between regions throughout the national system can be upgraded. The centers might be closely linked to research institutes that are in the same geographical areas. Preferably, the selected region should be distant from Moscow and St. Petersburg, which traditionally have attracted more financial resources than other areas of the country. Such outreach beyond the two principal cities of Russia would certainly command attention throughout the country.

The two centers would be an important step in establishing standards for upgrading the entire SSESC network over the long term. Further, because SSESCs are the primary organizations for reporting disease trends and outbreaks, particularly at the local level, they are an essential resource for supporting the surveillance oversight at the excellent facilities in Moscow. Their interactions with the highly experienced Moscow center should also benefit the model centers.

The model centers should be internally linked via electronic communications with SSESCs throughout the country. The entire system should be externally linked with the WHO and other nodes of the international disease surveillance community. The model centers should have surge capacity to address outbreaks and other crisis situations not only in their own geographical areas but also in nearby regions of the country while providing up-to-date information to Moscow. Also, the centers could become regional and local training centers.

Regardless of their locations, significant investments will be required to establish the centers, either through upgrading existing facilities or constructing new facilities. Still larger investments will be required to upgrade additional centers based on lessons learned at the model centers. Important capabilities of the proposed regional model center are set forth in Box 2.1.

The center at the local level would have more modest capabilities building on those that may already be available in the area. Modern diagnostic capabilities and communication facilities would be key components at both centers. New

BOX 2.1
Capabilities of the Proposed Model SSESC at the Regional Level

- Monitoring infectious disease trends and investigating outbreaks
- Coordinating the delivery of vaccines
- Isolating, characterizing, and identifying naturally occurring infectious agents using BSL 2 and BSL 3 laboratory containment capability as necessary
- Using polymerase chain reaction techniques and employing microbial and viral culture technologies for preliminary characterization of pathogens
- Developing and maintaining reference reagents for known endemic disease agents
- Safely and rapidly packing and shipping specimens and transporting them to an appropriate facility for further investigation
- As a reference laboratory, distinguishing between known pathogens and unusual isolates
- Recognizing and characterizing anthrax, plague, tularemia, smallpox, viral hemorrhagic fever, and other highly dangerous disease agents
- Implementing programs of polio eradication and measles elimination, as well as controlling and responding to influenza
- Determining infectious causes of unexplained deaths, encephalitis, febrile rash illnesses, and other diseases

personnel needs would depend on the capabilities currently existing at the selected locations.

Special allocations of funds, either from the Russian government or from a combination of government and international sources, will be needed to establish the model centers since the investment costs for the two centers will be significant, perhaps totaling in the tens of millions of dollars or more each. However, this level of funding is very small in comparison with the funds required to upgrade the entire SSESC system of 2,300 facilities. As the Russian economy continues to improve, new funds for much wider improvements throughout the system will likely become available from the government budget. The experiences with the model centers can provide important and persuasive long-term guidance on how other facilities can best use resources they now receive or will receive in the future. Such guidance is important to ensure consistency within the system.

In developing the recommendation to upgrade the SSESC system through the establishment of two model centers, the committee considered three other options as targets for initial investments that may become available. All of the other options were considered less promising means of launching a large-scale upgrade of the entire system of 2,300 centers. The three alternatives considered were as follows:

• Additional funding directed toward upgrading communication networks throughout the entire system. While improved communication is important and needed, more complete and authoritative information sent over the existing networks is an even more critical need, particularly in the long term. Experts at many of the centers know what is required to improve communication and are taking steps to help remedy the situation. However, upgrading their other activities is stymied not only by the lack of funding but also the inability to determine which improvements are needed and which are of highest priority.

• Additional funding spread across the 89 regional centers, enabling them to focus on the most pressing needs in their particular regions. Determining how best to divide funds and then account for their use would be difficult and might well destroy the program before it started. Also, it is highly unlikely that the performance of many SSESCs would be significantly improved in the absence of an unrealistically massive influx of funding. Finally, there would be little likelihood that an attractive standard for nationwide emulation would be achieved.

• Additional funding spread across six to eight SSESCs, which would become "partial" model facilities. This approach is less likely to have nationwide impact than the chosen alternative. As has been demonstrated at the center in Moscow, government officials at the national and local levels and the general public are more impressed by a "complete package" of modern technology as a goal than by partial measures. Unfortunately, because Moscow is widely considered a special case with nearly unlimited funding support, that center cannot effectively serve as a model. However, two modern centers in distant cities would attract considerable attention as realistic models for the rest of the country.

Turning to a second recommendation, despite the strong field capabilities of Russia's anti-plague system, it has remained organizationally distinct from the system of SSESCs and somewhat detached from Western efforts to improve surveillance and response capabilities in Russia. Further, there has been little progress in efforts to harness the resources of the anti-plague system to serve broader global interests. Still, the system continues to be an essential component of Russian efforts to counter infectious diseases. Therefore these facilities are in a unique position to lead investigations of outbreaks under a variety of environmental conditions that would be of interest to the broader international community.

Thus, **the second recommended initiative is directed toward fully integrating Russia's anti-plague network into the national public health surveillance system and then into global systems.** Even though the Russian anti-plague monitoring facilities have remained largely isolated from the international community, perhaps due to security sensitivities dating from the Soviet era, they continue to be an essential component of Russian efforts to prevent and control infectious diseases of local, national, and global interest. Their data banks and their strain collections are valuable resources and should be fully utilized in building modern disease prevention and control programs that include geographic monitoring, laboratory diagnosis, reference identification, and intervention.

Transformation from an internal to an external orientation could begin with modest investments to update disease surveillance within Russia by improving the equipment and communication capabilities of the five anti-plague institutes and then moving toward international cooperation. It is likely that, if asked, the international community would contribute some of the necessary funds, given the worldwide benefits of such a transformation. The initiation of joint U.S.-Russian epidemiological systems would be a logical early step in this direction.

Upgrading the SSESC system and bringing the anti-plague network more directly into national and international surveillance systems are only two possible initiatives to strengthen Russia's surveillance and response capabilities. Certainly greater support of agriculture disease surveillance networks with special attention to zoonotic diseases would be highly beneficial as well.

The next chapter addresses the role of research organizations which support surveillance and control activities described in this chapter. Together, these two chapters should provide useful guidance for further Russian efforts to improve the scientific base for combating infectious diseases.

3

Pillar Two: Meeting Pathogen Research Challenges

Effective surveillance and response programs of industrialized nations must be supported by a solid research base that draws not only on the capabilities of researchers within the country, but also on the findings of the broader international scientific community. Research is particularly important when considering those infectious agents that are newly identified, either within nature or as the result of bioterrorism-related activities. At the same time, there are many unanswered questions concerning even common disease agents.

Coupling solid fundamental research with targeted applied research is also beneficial to Russia's national goals and those of the international community in the biosciences and public health. Specifically, applied research efforts can help:

- evaluate test methods and other tools, including epidemiology and forensics, to identify and understand endemic and newly emerging infectious agents of human and agricultural importance
- identify the behaviors, environments, and host factors, including chronic diseases, that put people and animals at risk of infections
- develop and evaluate prevention and control strategies, including disinfectant approaches, vector control measures, and the use of vaccines and drugs

Such applied research activities build upon the results of fundamental research activities conducted both domestically and internationally (CDC, 1998a; Maksimova, 2003).

RUSSIAN RESEARCH INSTITUTIONS

For decades, the Soviet and then Russian governments have supported many dozens of large public research institutes with programs that address the foregoing and related challenges of infectious diseases. Appendix J identifies a number of the principal research institutes that are currently involved in this large national effort. Most are under the jurisdiction of the Ministry of Health and Social Development, the Ministry of Agriculture, the Russian Academy of Sciences, the Russian Academy of Medical Sciences, and the Russian Academy of Agricultural Sciences. A few that were previously state institutes have been privatized, although the government retains a substantial percentage of ownership in some. In addition, a number of Russian universities and other institutions of higher education have important biological research activities. A handful of commercial organizations, such as those in the veterinary sciences, are also beginning to recognize the importance of supporting applied research at universities.

Most Russian research institutes relevant to this study have applied research programs designed to directly support public health or agricultural activities. A few are oriented toward developing products for the commercial marketplace, although most continue to look to government organizations as their principal clients—and therefore the funders—of research. As indicated in Appendix J, a few institutes have been designated by the government as State Research Centers with access to special funds available through the Ministry of Education and Science.

One of the largest centrally coordinated research efforts in the field of infectious diseases directed toward the improvement of general approaches to disease prevention and control was organized by the former Ministry of Health and is now under the purview of the Ministry of Health and Social Development. Several research institutes of the ministry and numerous institutes of the Russian Academy of Medical Sciences are involved (see Appendix J). The following research areas have received primary attention:

- fundamental and applied research in medical microbiology, virology, immunology, epidemiology, parasitology, and disinfection
- improvement of the nationwide epidemiological surveillance system (previously discussed in Chapter 2)
- development of new preparations and methods for diagnosis, vaccine prophylaxis, and drug-based prophylaxis
- improvement of the prevention system and anti-epidemic measures consistent with regional characteristics of infectious pathology

This program has claimed many successes even in recent years when budgets were severely constrained. Specifically, Russian officials point to the following successes: the development of several dozen new medical vaccines and drugs now in various phases of investigation; the preparation of approximately 50 sets of methodological instructions and recommendations; the publication of 40 handbooks for physicians; and the promulgation of a dozen regulations and rules to protect sanitary conditions in the research environment. About 100 applications for Russian patents developed within the framework of the program have been approved or are in the approval process. Appendix K describes other recent achievements of the program (Onishchenko, 2002).

Also worthy of mention in the context of disease-related research is the complex of research and production facilities that retain a relationship with Biopreparat (see Appendices J). Biopreparat is best known for its Soviet era role in biodefense activities. In the early 1990s, the Russian government redefined its mission to develop and produce medical products, primarily for the Russian market. The Biopreparat complex has been largely privatized with the Russian government retaining a significant number of shares in most institutes, which now are loosely affiliated with the Ministry of Health and Social Development. The Institute of Applied Microbiology in Obolensk and the Institute for Applied Biotechnology and Virology "Vector" in Koltsovo report to the Federal Service for Surveillance of Consumer Rights Protection and Social Welfare, a division of the Ministry of Health and Social Development. This should enhance the research and diagnostic capabilities of that service.

Most, if not all, of the Biopreparat institutions were involved in Soviet biodefense programs until the early 1990s under the USSR Ministry of Medical and Microbiological Industry. At their peak, they employed tens of thousands of scientists, engineers, technicians, and service personnel. With lucrative funding, they developed strong capabilities that are relevant to infectious disease diagnosis, prevention, and therapy. Government-sponsored programs should draw more broadly on the underutilized research capabilities of Biopreparat institutions, as the researchers become more acclimated to working with colleagues from other Russian institutes that have always been civilian oriented.

An important research priority at the Biopreparat institute "Vector" is the investigation of smallpox. This disease has been identified by the Russian government as a serious bioterrorism threat. For many years, Russia has hosted one of the two worldwide repositories for smallpox strains. Russian officials believe that their researchers can make significant contributions in characterizing smallpox and assisting in developing antidotes which would be very important in responding to an incident should illegally obtained strains fall into the hands of terrorists.

Turning to the agricultural system, the Ministry of Agriculture has several relevant research institutes under its direct control. For example, a veterinary sciences institute in Vladimir is studying foot-and-mouth disease; another in Kazan, brucellosis; and a third in Pokrov, rabies and related diseases. Under the Russian Academy of Agricultural Sciences there are all-Russian institutes, zonal institutes, and veterinary research stations that further extend disease-related capabilities (see Appendix J for a list of institutes).

TABLE 3.1 Evolution of Regulatory Framework for Genetic Engineering in Russia

Year	Regulation
1996	Federal Act "State Regulation of Genetic Engineering Study," Adopted
2000	Federal Act "State Regulation of Genetic Engineering Activity," Amended
2000	Instruction by Chief State Sanitary Physician of Russia "Hygienic Expertise of Food Products Derived from Genetically Modified Organisms," Issued
2001	Order by Government of Russia "State Registration of Genetically Modified Organisms," Issued
2002	Order by Government of Russia "State Registration of Feeds, Derived from Genetically Modified Organisms," Issued
2003	Order by Chief State Sanitary Physician of Russia "Microbiology Molecular-Genetic Expertise of Genetically Modified Microorganisms Used in Food Production," Issued

SOURCE: Center for Bioengineering, Russian Academy of Sciences (November 2003).

As for plant protection, ministry institutes address broadly defined disease and quarantine issues. Institutes under the Russian Academy of Agricultural Sciences conduct research for the optimization of phytosanitary conditions based on integrated pest management, chemical control, and biological control. The principal research institutes in this field are listed in Appendix J.

In the relatively new research area of genetically modified organisms (GMOs), more than 80 institutes and higher education institutions have established research review committees, indicating widespread interest in this frontier area of science. As the result of a nationwide competition for cutting-edge projects in all fields of applied research in the spring of 2003, the former Ministry of Industry, Science, and Technology awarded a substantial grant to the Bioengineering Center of the Russian Academy of Sciences for work on genetic modifications of potatoes, sugar beets, soybeans, and other crops with disease-resistance being one of the objectives (for a list of other proposed projects, see Appendix L). Table 3.1 identifies the key Russian laws on GMOs.

Finally, the Russian Academy of Sciences has traditionally played the leading role in fundamental science, particularly in microbiology, biochemistry, and virology. In the last few years, however, the pressure of drastically reduced budgets forced some of the academy's institutes to reorient much of their basic research toward more practical applied activities. Some have been successful in attracting domestic and international funding to support efforts with near-term applications, but a few institutes remain focused almost exclusively on basic science. Appendix J identifies a number of institutes with programs relevant, directly or indirectly, to infectious diseases. Many of the Academy's strongest biology institutes are in the city of Moscow and in the Pushchino area of the Moscow region.

DECLINE IN RUSSIAN RESEARCH CAPABILITIES

Unfortunately, since 1990 one of the primary metrics for determining budgets of government research organizations, including academies of sciences and ministries with affiliated research institutes, has been the number of their institutes dependent on federal funds and the number of employees within these institutes. Too often quality and significance of research have been set aside in favor of maintaining the largest possible payroll. According to some Russian scientists, this is a widespread approach among Russian research managers, particularly the older generation, who believe they have a social responsibility to their staff members that have no employment possibilities beyond current positions, however depressed pay scales may be.

Still, during the past decade, almost all Russian research institutes have experienced significant downsizing as many of the most entrepreneurial scientists have found better paying jobs elsewhere. In some, the scientific staff has been reduced by more than one-half. A number of the best researchers, faced with evaporating salaries and malfunctioning equipment, have either abandoned their scientific careers or moved abroad in search of opportunities to continue working at the frontiers of science. The flight of scientists is discussed in more detail in Chapter 5.

In Russia's research institutes, the base salary of laboratory directors in 2003 was equivalent to about $200 per month and that of senior scientists $150 per month, far less than industrial workers received for example. Some entrepreneurial researchers were able to supplement these base salaries with income from international or Russian grants, but many researchers and support staff did not have access to salary supplements. As for equipment, one estimate indicates that most institutes had less than 65 percent of the laboratory bench instruments needed for effective fulfillment of their research programs, 75 percent of the needed computers, and 10 percent of the required large equipment (Zverev, 2003).

On average, the government provides about one-half of the operating budgets of state research institutes; those budgets have less purchasing power than in the Soviet era (see Figure 3.1 for an indication of the relative low priority accorded research in the medical sciences in Russia today). The special programs of various ministries, international grants, one-time equipment allocations by the government, and the income from rental space and health-related services offered at the facilities cover most of the remaining 50 percent.

Examples exist of both financially stable research institutes—such as the Institute of Highly Pure Biopreparations, the Englegardt Institute of Molecular Biology, and the Institute of Epidemiology—and institutes that have approached the brink of bankruptcy, for example, the State Research Center for Applied Microbiology in Obolensk. The sharp rise in the cost of electricity poses a pressing financial problem for almost all institutes with no easy solution. Often, in order to pay energy bills, institutes reduce scheduled purchases of needed modern laboratory equipment or even reduce the working hours at the facilities.

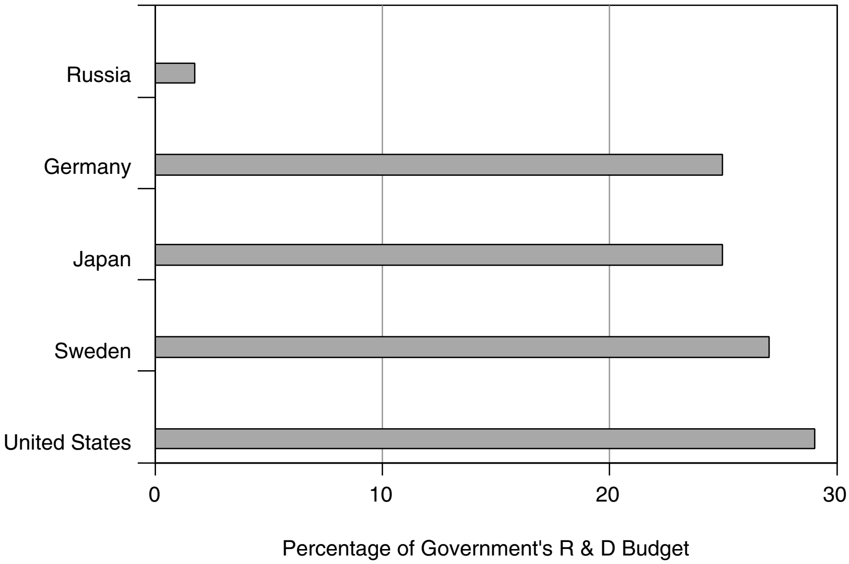

FIGURE 3.1 Medical sciences share of government-sponsored academic R&D. SOURCE: Science and Engineering Indicators, National Science Foundation (2004).

But financial constraints on domestic activities are not the only problem confronting Russian research institutes. Participation in activities of the international scientific community also presents enormous difficulties. First, coordination with the activities of the international community is sometimes weak, and at times experiments already conducted abroad have been repeated unnecessarily in Russia because international publications were not available during the design of Russian experiments. Second, export control barriers hamper exchanges of biological materials, strains, technologies, and genomic databases. The United States is the strongest proponent of stringency in protecting these items that could be of interest to terrorist groups. But as Russia tightens export controls, foreign partners are increasingly denied access to Russian resources. Third, while Internet access is becoming more commonplace in Russia, few funds are available for attendance at international conferences or for short study trips abroad.

ADVANCING LABORATORY RESEARCH

Russian colleagues have admirable ambitions for elevating Russian research to the global level in the future. They recognize that applying advances in nanotechnology, new materials, and information technology to biotechnology, for example, could create systems and devices with large benefits for health, personal safety, business, and trade. They advocate the need for Russian researchers to concentrate on daunting challenges such as

- DNA sequencing and analysis for molecular diagnosis of diseases, identification of molecular markers, disease prediction through gene typing, and genetic methods for combating diseases
- GMOs not only for agricultural crops but also for the production of insulin, interferon, and edible vaccines
- use of high-resolution physical methods to develop new approaches to therapy for controlling the immune system and overcoming drug addiction
- engineering for treatment of heart disease and for xenotransplantation of organs, tissues, and cells, including those from genetically modified animals

They point out that it is better for Russian scientists to be working on these topics in collaboration with international colleagues than to be caught by surprise by discoveries of international colleagues (Sandakhchiev, 2003).

Although this is a laudable agenda, it would stretch current Russian capabilities beyond realistic near-term limits. Conducting frontier research in more traditional areas, let alone undertaking internationally competitive efforts in advanced fields of science, will require concerted efforts by the best laboratory teams in the country. These teams need substantial financial support, primarily from the Russian government.

Unfortunately, many of the strong research teams of the past have disappeared and have not been replaced. Those that have remained in place have been weakened by the loss of experts and the degradation of equipment capabilities. Nevertheless, there are still areas of very strong Russian research capability. However, in the absence of much greater and more highly focused government efforts to adequately support even a limited number of research teams, Russian research will have declining significance for the international community and for Russia.

Because the Russian government is unable to provide an adequate level of support for its large complex of research institutes in the near term and possibly even in the long term, the Ministry of Education and Science has proposed closing the less productive research institutes and redirecting these funds to the stronger ones. Closing institutes is difficult for both political and social reasons. Strong arguments exist for maintaining broadly based research capabilities to address infectious diseases in different ecological zones. Also, no local politician is prepared to accept closure of an institute in his or her region since most employees of institutes have no other places for employment and little opportunity to relocate.

The government's designation of a few institutes as State Research Centers one decade ago and the promise to channel substantial special funds to these institutes was an attempt to support the best scientific teams to the fullest extent possible. However, the anticipated funding levels were not realized, and the selection of entire institutes that may have had hundreds of unproductive scientists dependent on the high productivity of outstanding scientific coworkers proved to be an ineffective approach. In addition, in open competitions, Western funders frequently select recipients of grants based on the quality of the achievements by individual researchers rather than on the status of his/her institute. At the same time, most external funders are so focused on near-term project results that they do not adequately consider the long term viability of the institutes' laboratories and supporting infrastructure.

The approach of focusing on laboratories of excellence advocated by the committee does not call for closing other research entities, which of course is a significant issue that can only be addressed by the Russian government. Focusing a significant portion of available resources more sharply on the most promising research groups should enable these laboratories to undertake additional programs of public health importance and thereby foster high standards of achievement. In time, this approach may put pressure on traditional funders to reduce support for less productive groups. Such reductions of support might lead to the consolidation or closing of laboratories that are not productive, thereby releasing additional funds for more productive programs. Competition between researchers for resources would stimulate productivity, regardless of the level of available resources. The alternative approach of continuing to spread available resources over laboratories in all relevant research institutions, would continue a tradition that has led to the current decline in research productivity throughout the country and inadequate support of public health needs.

Against this background, the committee recommends an expanded effort by the Russian government, with the assistance of external funders, to focus laboratory research in order to more effectively advance public health and the control of agricultural diseases.

First, it is important to concentrate financial support on carefully selected research groups that are, or have the potential to become, centers of scientific excellence. Several hundred key Russian laboratories, each of which employs one or more integrated groups of scientists working toward common goals are, or could be, core elements of the Russian public health and agriculture research infrastructures of the future. Such important laboratories warrant special financial support granted through a competitive peer review process to enhance the research programs of their research groups.

Criteria for determining special financial support might include: (1) scientific excellence and relevance of research activities to public health and agricultural priorities of the government; (2) recent achievements of the research groups in advancing specific areas of science and in contributing to important human, animal, and plant disease prevention and control programs of the Russian government; (3) demonstrated capabilities of the scientific staff, particularly the rising young scientific leaders within the research groups; and (4) a tradition of cooperating with and facilitating the development of other Russian research groups with related interests.

A second initiative is to upgrade facilities and equipment for appropriate disease-related research at selected laboratories throughout the country. Recent emphasis in Russia on using limited available funds primarily to meet payrolls has been accompanied by a dramatic decline in the facility and equipment assets of research institutions, including capabilities to maintain and disseminate data and to communicate rapidly domestically and internationally. As noted, increasing energy costs will further divert funds from support of equipment needs. This erosion of equipment capabilities has, in turn, contributed to a loss of Russian competitiveness in the search for international financial support as well as a decline in research productivity. Meanwhile, many of the best Russian scientists have emigrated to foreign laboratories where they can work using modern equipment.

The costs of adequately equipping even the several hundred laboratories which would house centers of excellence would be very high, and the primary source of funds must be the Russian government. Therefore, a fair and open competitive process for selecting recipients of funding is essential. This process should lead to a concentration of modern equipment to support the strongest research groups. Training to ensure optimum use of equipment would also be an important component of programs that provide equipment.

Laboratories that house research groups may normally compete for equipment and facility grants although on occasion, it may be appropriate for an entire institute to seek large grants that support activities in several laboratories. In addition, individual research groups would compete for research grants. The research centers of excellence would therefore emerge as the result of success in these two types of competitions.

With several exceptions, Russian ministries, agencies, and academies currently provide research funds to institutions, not directly to research groups or laboratories. Institute directors then play a central role in determining how funds are allocated within the institute. However, this central control has been weakened considerably during the past decade as many external funders now allocate funds directly to research groups and even to individual researchers with the approval of institute directors. The recommendations in this report, if implemented, should follow this new pattern. Reluctance of most directors to allow direct funding of their research groups should, in most cases, dissipate when their researchers have opportunities to compete for funds that would not otherwise be available.

As indicated in Box 3.1, some institute directors need no encouragement to embrace centers of excellence. But there have been examples of other institute directors refusing funding that they could not personally control; there are also examples of merit-based Russian grant competitions degenerating into programs

BOX 3.1
Support for Centers of Excellence

"If an institute director is interested in advancing the agenda of his own institute as a whole and has talent for pursuing that objective, then the director will not really have to be guided forward through any laboratories-of-excellence-type mechanism. In fact, there will certainly be prototypes of such laboratories already functioning in his institute."

SOURCE: Russian manager of biological research programs (October 2004).

that have stretched grant funds so widely in an effort to support as many researchers as possible that individual grants have had little impact. There are counter examples of institute directors who have fully supported direct grants to individual researchers. This is evidenced by the Russian directors of dozens of institutes involved in infectious disease research who have endorsed grant payments by the International Science and Technology Center in Moscow directly to thousands of Russian researchers in their institutes.

These steps can contribute to developing the modern scientific basis that will enable Russia to work more effectively with the international community to implement an infectious disease research agenda that contributes in new ways to understanding the role of genetic, environmental, clinical, social, and economic factors in the emergence of diseases.

Sources of financing are the essential aspects of these recommendations. A realistic approach to funding these recommendations for an initial period of five years would be a combination of Russian government resources and a loan from the World Bank or the European Bank for Reconstruction and Development. The World Bank has in the past, when requested by host governments in Central Europe and other regions, provided loans in the tens of millions of dollars to support research grant programs and programs for upgrading scientific infrastructures.

Should one of these development banks be asked by the Russian government to support the approach of selective financing for centers of excellence, few directors of high quality Russian institutes are likely to remain resistant, entrenched in past approaches. The stakes would be too high not to participate. Those directors who sit on the sidelines would soon become recognized as working on the basis of evaporating hopes of the past and not the basis of present and future realities. Even if the banks are not responsive due to Russia's improved economic condition, the Russian government itself is becoming an increasingly likely source of new financial support for such efforts.

In summary, there is a clear need to change current patterns of Russian funding for research in biology and other disciplines relevant to controlling infectious diseases. An important criterion for the allocation of available resources to research groups is their likely impact not only on scientific advancement but also on economic and social progress. No longer can science be simply an afterthought in the funding process with allocations based on "whatever-is-left-over." Rather, to be leaders, the Russian scientific community needs to show in very specific and persuasive ways how it is making major strides toward meeting the health-related needs of the Russian people.

4

Pillar Three: The Promise of Biotechnology

As the context for Russian industrial activities steadily incorporates principles of market economics, many public and private customers for pharmaceutical products are continually reconsidering which products they purchase and at what prices. An abundance of imported products are readily available in Russia while consumer confidence in goods made in Russia has declined. Russian scientists and manufacturers are having difficulty keeping pace with advances in technology throughout the world. Thus, it is not surprising that domestic enterprises which manufacture products for protecting human health are operating at less than 25 percent of capacity and that many production lines are now outmoded. Similar problems exist in the agricultural sector where government support of state enterprises has also greatly declined.

This chapter provides a brief overview of the commercial and regulatory environment for the pharmaceutical/biotechnology sector as it develops in Russia. There is considerable interest in Russia in developing and producing vaccines, drugs, test kits, and other products for both the domestic and international markets. But the challenges are formidable, and Russia is far behind many other countries in reaching international customers. Nevertheless the committee has observed encouraging signs of new entrepreneurship and believes that during the next decade, Russia will begin to emerge as a significant contributor in this field, probably relying heavily on joint ventures with international companies. While imported products will continue to have a major presence in the Russian pharmaceutical/biotechnology market, a stronger domestic presence should improve the overall infrastructure for more effectively combating infectious diseases in the country.

Further, this chapter first describes the Russian marketplace for drugs, vaccines, and test systems. It highlights the role of the Biopreparat complex, which was a focal point for Soviet defense-related activities, and the role of Biopreparat-affiliated institutions in cooperative U.S.-Russian nonproliferation research programs. After noting some of the key aspects of the evolving regulatory framework in Russia, it highlights the gap between research activities sponsored by the Russian government and commercial production activities. It then offers several suggestions for facilitating development of the biotechnology sector in Russia.

THE MARKET FOR MEDICAL PRODUCTS IN RUSSIA

Medical Products for Humans

According to Russian estimates,[1] the market in Russia for drugs intended for human consumption (valued at the point of use) rose from $2.5 billion in 1999 to $3.7 billion in 2002, with a projection of $5.0 billion in 2005. This growth has been attributed largely to higher consumer earnings. About 60 percent of the costs were carried by consumers. Various state organizations covered the remaining 40 percent. About 70 percent of drugs were distributed by prescription and 30 percent were over-the-counter items. Approximately 70 percent of drugs (by cost) were imported. This figure reflects the emphasis of Russian producers on cheap generics while expensive specialty drugs largely come from abroad. Among the principal obstacles to the further development of markets in Russia—both for foreign and domestic manufacturers—are a lack of transparency in the registration, certification, and licensing systems; inadequacies in the protection of intellectual property; and the large quantity of counterfeit medicines.

Of the top 20 producers of drugs in Russia in 2002,[2] only two companies were Russian-owned: Akrikhin (also known as Otechestvennoe Lekarstvo) and Marbiofarm, the Russian branch of Valeant Pharmaceuticals International (formerly ICN Pharmaceuticals). Other Russian producers were Firma Bryntsalov and Moskhimfarmpreparaty. As for imports, the market has become less concentrated, with the total market share of the top five importing companies decreasing from 25 percent in 2001 to 19 percent in 2002 (Maksimova, 2003).

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[1]This discussion is based on estimates contained in TEMPO Noncommercial Partnership Center of Modern Medical Technology (2003). A report by the U.S. Embassy in Moscow has somewhat different estimates, although in a general sense the estimates and the trends are similar as noted in Maksimova, 2003.

[2]These drug producers are, in descending order: Aventis, Gedeon Richter, KRKA D.D., Berline-Chemie/Menarini Pharma, Sanofi-Synthelabo, ICN–Russian Plants, GSK, Novartis, Servier, Pliva, Nycomed, Lek D.D., Bristol-Myers Squibb, Dr. Reddy’s, Pfizer, Janssen-Cilag, Egis, Akrikhin, Balkanpharma, and Boehringer Ingelheim (TEMPO Noncommercial Partnership Center of Modern Medical Technology, 2003).

Domestic production of vaccines for use in humans increased to a sales level of $48 million in 2002 from $44 million in 2001. Meanwhile, imports decreased from a value of $52 million in 2001 to $33 million in 2002. The fluctuation in imports is partially explained by increased sales in 2001 in anticipation of new taxes in 2002, and then a decline in 2002 as a result of those taxes. Only a very small fraction of sales were to pharmacies and hospitals (7 million rubles or about $225,000), because vaccinations are administered primarily in polyclinics, preschool and school health facilities, and medical centers of enterprises. Important anti-viral vaccines produced in Russia are identified in Table 4.1, and manufacturers are identified in Table 4.2. Tables 4.1 and 4.2 provide a summary overview of the limited vaccine production in Russia and suggest that there are considerable opportunities to increase such production.

In short, the value of vaccines produced and consumed in Russia is very small in comparison with the value of drugs. Yet, according to the Russian Academy of Medical Sciences, research efforts devoted to vaccines far exceed the extent of research on drugs, highlighting the disconnect between research and commercialization of products. While the research on vaccines is important, there should also be important new opportunities to expand drug-related research in support of the Russian-based pharmaceutical industry.

As for diagnostic test systems, domestic production was estimated at $16 million in 2002, 31 percent higher than in 2001. Imports remained steady at about $5 million. The increase was initially largely attributed to a growing demand for HIV/AIDS test systems. Purchases by the Russian government of HIV/AIDS test

TABLE 4.1 Important Anti-viral Vaccines Produced in Russia, 2002

Vaccine	Sales (millions of U.S.$)	Share of Sales (percent)
Viral hepatitis B, Recombinant DNA	20.0	42
Influenza, trivalent polymer-sub-isolated, liquid (Grippol)	5.7	12
Anti-rabies	2.6	5
Tick-borne encephalitis, cultured, cleaned, concentrated, inactivated, dry	2.5	5
Mumps, cultured, live, dry	2.3	5
Influenza, allantois, live, intranasal, for children	1.9	4
Poliomyelitis, peroral 1, 2, and 3 types	1.7	4
Mumps-measles, cell-cultured	1.7	3
Measles, cell-cultured	1.6	3
Viral hepatitis A	1.3	2

SOURCE: TEMPO Noncommercial Partnership Center of Modern Medical Technology, 2003. Also, www.gsen.ru lists all vaccines licensed in Russia, both domestic and imported. These include diphtheria, tetanus, and pertussis, for example.

TABLE 4.2 Leading Producers of Vaccines in Russia, 2002

Producer	Sales Volume (millions of U.S.$)	Share in Vaccine Sales Volume (percent)
Solvay Pharma	4.28	48.9
GlaxoSmithKline	1.33	15.2
Immunopreparat	0.55	6.3
ICI Pharmaceuticals Inc.	0.49	5.6
Pasteur Merieux Connaught	0.44	5.0
Virion	0.32	3.6
St. Petersburg's Scientific Research Institute of Vaccines and Serums	0.19	2.2
Institute Merieux	0.11	1.3
Chumakov Institute of Poliomyelitis and Viral Encephalitis	0.06	0.7
Chiron Behring GmbH and Co.	0.04	0.5

SOURCE: TEMPO Noncommercial Partnership Center of Modern Medical Technology, 2003: 21.
NOTE: The producers are primarily foreign-owned companies which generally have higher sales (by cost) due to the higher prices charged than those charged by Russian manufacturers. The following domestic manufacturers produce limited quantities of vaccines: Vector (measles and hepatitis A); Enterprise for Production of Bacterial and Viral Preparations, Moscow (measles and mumps); NPO BIOMED, Perm (DPT); COMBIOTECH, Moscow (hepatitis B). In addition, the Microgen State Unitary Enterprise links about 20 production facilities which produce a substantial portion of Russia's vaccines.

kits has not increased significantly in the past several years, however; but there has been an increase in the assortment of test kits offered, including those for polymerase chain reaction systems.

A small percentage of test kits has been sold through pharmacies and hospitals. Most are purchased through state procurements for health departments and polyclinics. Twenty percent of sales were directly related to infectious diseases. Among the 20 companies in Russia that produce diagnostic kits of good quality are BIOSERVICE (Moscow), Diagnosticheskie Sistemi (Nizhnii Novgorod), ECOLAB (Moscow Region), and MBS and VECTOR-BEST (near Novosibirsk). These and others are listed on several Web sites (www.fcgen.ru; www.vector-best.ru; www.npods.ru; www.mbu.ru; www.mbu.ru; www.ekolab.ru). Appendix M identifies some of the many test systems currently manufactured in Russia.

Sales of products related to the treatment of prevalent human diseases are as follows. Domestically produced preparations for treating hepatitis rose considerably from 2001 to 2002, with vaccines increasing 150 percent and immunomodulators four-fold. Sales of both domestic and imported tuberculosis diagnostic preparations fell considerably from 2001 to 2002. Although the value of sales to pharmacies and hospitals increased, this growth largely reflected an increase in

BOX 4.1
The Biopreparat Production Complex (2003)

The Joint Stock Company Biopreparat integrates 20 industrial enterprises that manufacture one thousand different products. The annual volume of commodity output, which is increasing, amounts today to over 10 billion rubles per year. Biopreparat accounts for nearly 35 percent of Russia's total output of medical products, valued at more than 8 billion rubles in drugs and 1.7 billion rubles in medical engineering articles. Over 36,000 people are engaged in production. In Russia, Biopreparat leads in manufacturing certain drugs such as antibiotics and substances for their production, organic preparations, infusion solutions, and blood substitutes.

The following companies fall within the Biopreparat complex: "Sintz" Joint-Stock Commercial Company, Kurgan; "Moskhimfarmpreparaty" FGUP, Moscow; "Biosintez" Open Joint-Stock Company, Penza; "Biokhimik" Open Joint-Stock Company, Saransk and; "Krasfarma" Open Joint-Stock Company, Krasnoyarsk.

NOTE: Exchange rate in 2003 was approximately 30.7 rubles = $1.

SOURCE: Adapted from BIOPREPARAT booklet obtained in Moscow in June 2003.

taxes. Diabetes treatment drugs represent one of the fastest-growing segments of the pharmaceutical market, even though imports continue to dominate. Insulin makes up a large percentage of sales. Finally, cancer treatment preparations also represent a growing consumer demand, particularly for immunomodulators and hormone-free anti-tumor preparations (TEMPO Noncommercial Partnership Center of Modern Medical Technology, 2003).

Finally, the Biopreparat Complex (discussed more fully in Chapter 3) deserves particular attention in the discussion of Russia's pharmaceutical market since it has been a focal point for U.S.-supported nonproliferation programs. Box 4.1 highlights its industrial activities.

Of immediate concern to domestic producers of vaccines, drugs, and other medical products is the new Russian legal requirement that by 2005 all production facilities must comply with the regulations calling for Good Manufacturing Practices (GMP). Also, data supporting applications to produce new products must be based on work in laboratories complying with Good Laboratory Practices. Highlighting the problem, 10 domestic factories and institutes were producing different vaccines in 2003, but only one met GMP standards (Zverev, 2003).

Medical Products Related to Animals and Plants

Comparable data are not readily available on the production of vaccines and drugs for animal diseases. A major producer is the government-owned conglomerate RosAgroBioProm, which at one time had a dozen factories. Each factory employed hundreds and even thousands of workers. These factories have retained only a limited degree of stability during the economic slump of the past decade, and some are on the verge of bankruptcy. Appendix N identifies the principal production facilities of RosAgroBioProm.

The cornerstone legislation governing medicines in the agriculture sector, the Medicinal Drug Law, is the same as the legislation for medicines in the human health sector. Issues related to registration, certification, and selective control are very similar, as are the mechanisms of production certification, verification, and control of drugs. A Veterinary Council for Pharmacology and Biology serves as the regulatory body.

There are only a few manufacturers of animal medicines in Russia, and they are unable to satisfy market demand. RosAgroBioProm has eight operating plants, the Ministry of Agriculture has one institute producing medicines, and the Academy of Agricultural Sciences also has one such institute. In addition, four private companies are operating in Russia. Several joint ventures involve foreign partners (Bayer, Intervet, IDEXX, KPL), but they largely assemble raw materials from active ingredients produced abroad.

The government is a minor customer for agrodrugs, with the Ministry of Agriculture purchasing $3 million in drugs in 2003. The bulk of agrodrugs are purchased by privately owned agricultural enterprises or by joint stock companies.

While privatization of agricultural land has fallen behind other privatization efforts, practically all businesses engaged in animal husbandry are non-state organizations, specifically private enterprises and joint stock companies privatized in the early 1990s. Land is leased to these businesses on a long-term basis. Almost every animal for which veterinary services products are procured is privately owned.

Finally, the State Veterinary Service is very interested in high-quality drugs to ensure a favorable epizootic situation. While there may be concerns regarding the fairness of government procurement policies for vaccines and drugs, the Service seems determined to advance science in the direction of protecting animal health.

With regard to plant diseases there is only limited industrial capability to support plant protection programs. Most herbicides and insecticides are imported. Limited efforts are being made to develop green pesticides, using natural ingredients as an alternative to synthetically designed pesticides with severe environmental side effects. But, overall, the quality of Russian products falls behind those from abroad.

The Regulatory Framework

The laws and regulations governing the production and distribution of vaccines, drugs, diagnostic kits, and other medical products for application to humans and animals are extensive in Russia, as in other countries. Russian laws and regulations address areas of great familiarity to Western professionals in the field although many detailed requirements of implementation are unique to Russia. The many problems that new organizations, particularly those not linked to the government, encounter in understanding these regulations pose a formidable challenge.

The following topics are addressed by the Russian regulatory framework (TEMPO Noncommercial Partnership Center of Modern Medical Technology, 2003):

- registration of foreign and domestic drugs and annual certification of conformity to reference specimens
- licensing of trade in pharmaceutical products and associated quality control measures
- coordination of retail prices with government ministries
- import and export of drugs and precursors
- lists of vitally needed drugs that receive tax and other special considerations
- insurance policies for drug coverage
- clinical tests of drugs, including preliminary studies of properties, preclinical investigations, and clinical trials
- value-added taxes and exemptions for pharmacies and other organizations
- requirements for good manufacturing practices at production facilities
- advertising limitations
- intellectual property rights
- efficacy requirements

THE GAP BETWEEN RESEARCH AND PRODUCTION

As noted in this and previous chapters, many research institutes have been working on the development of new vaccines, drugs, diagnostic test kits, and other items. But a large gap exists between most research endeavors and successful commercial marketing of research products. Often, commercialization is an afterthought for researchers, occurring only when they realize that, unless their products attract customers, they will soon have to abandon their efforts. Few institutes address marketing challenges early in the research cycle, and seldom are research projects willingly abandoned because of marketing risk.

Well-managed and technically strong research institutes can provide an important component of the institutional framework for the development of a modern biotechnology industry in Russia. This industry will most likely rely heavily on medium-size firms, particularly those firms operating within research institutes. Many individual entrepreneurs have attempted to spin technologies out of institutes and develop market niches on their own. But in the absence of a supporting technical and administrative infrastructure, they have often encountered difficulties quickly. In contrast, an optimistic report on vaccine-development research at biotechnology institutes is presented in Appendix O.

At the other extreme, few large pharmaceutical companies are ready to invest in somewhat risky biotechnology activities, nor do they have the technical wherewithal to compete in frontier areas because of the risk represented by financial arrears. Figure 4.1 underscores the reluctance of Russian industry to support research on pharmaceuticals of any type.

An example of an institute that is finding a way to continue its research is Biokhimmash, which has specialized in designing production processes for a variety of biology-based products. Its 200 specialists work on a variety of products such as: (1) new drugs based on plant and animal cell cultures; (2) plant growth stimulators; and (3) veterinary medicines. During the Soviet era, Biokhimmash designed specialty production equipment for biodefense facilities. The institute is now part of Elevar, a construction-oriented company that has very profitably built food processing plants, breweries, and other facilities related to the strengths

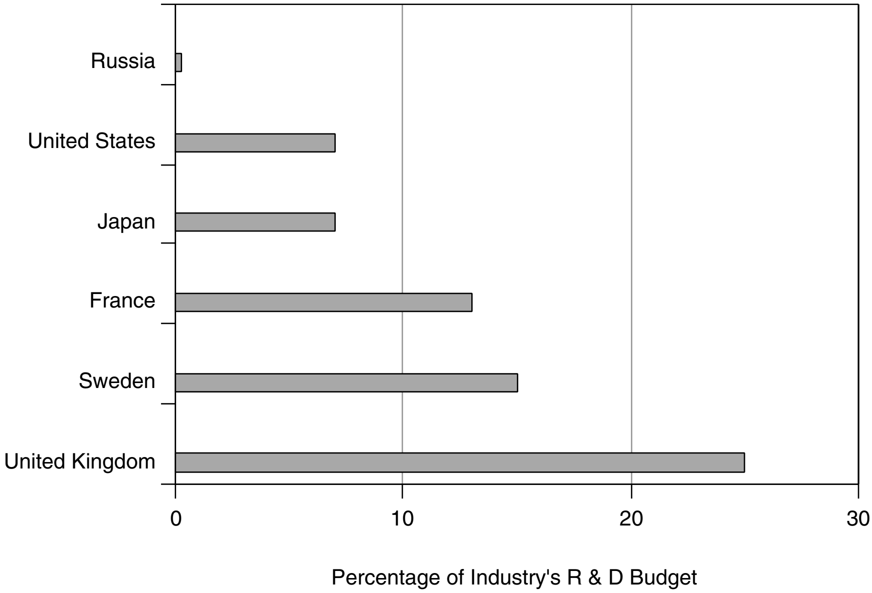


FIGURE 4.1 Pharmaceutical share of industrial R&D. SOURCE: Science and Engineering Indicators, National Science Foundation (2004).

BOX 4.2
Steps to Achieve Market Success for Insulin

- Development and patenting of technology
- Development of drug forms of short- and prolonged-action insulin
- Completion of preclinical and clinical trials
- Development of the state standard reference sample of genetically engineered insulin
- Development of the domestic sorbent for production of genetically engineered insulin
- Confirmation with standard sample and registration of the drug form of genetically engineered insulin
- Construction of an experimental production line for 10 kilograms of insulin a year
- Development, with a foreign partner, of a business plan and the technical-economic basis for construction of a factory with a capacity of 200 kilograms a year

SOURCE: Natsionalnie Biotechnologii (2004).

and interests of Biokhimmash. Elevar is prepared to use construction profits to support research at the institute, which over time should produce breakthroughs of commercial significance (Biokhimmash, 2003: 6).

A second example of institute scientists finding a market niche is the production of insulin by the firm Natsionalnie Biotekhnologii. With Gazprom acting as the principal investor, this firm made the journey to the marketplace from 1996-2002, at a cost of $9.3 million, as shown in Box 4.2.

A handful of other health-related biotechnology investors are active in Russia. For example, Medical Technology Holding is a daughter company of the huge conglomerate Sistema. It has an impressive array of financial sponsors and intends to engage in full-cycle drug production, from research and substance synthesis to production and distribution of the final products. It began with diagnostic kits for viral hepatitis B and HIV, hormones, and markers; currently it is expanding into other high-tech areas. The company has its roots in the scientific capabilities of the Gabrichevskii Scientific-Research Institute of Epidemiology and Microbiology.

In agriculture, the firm NARVAC was established on the premises of the Ivanovskii Scientific-Research Institute of Virology. It produces a variety of animal medications and food supplements. It is funded by a few individual investors, and the forecasts for commercial success are positive. Other firms in a number of cities are also targeting the agriculture sector as a consumer of new biotechnology products, but few have the modern facilities that are available at NARVAC.

It will be difficult, but important, to develop a substantial domestic biotechnology industry that initially will serve the markets of Russia, the former Soviet states, and more broadly, the world.

DEVELOPMENT OF AN INTERNATIONALLY COMPETITIVE BIOTECHNOLOGY SECTOR

The committee underscores the importance of the Russian government and its international partners in the development of an internationally competitive pharmaceutical/biotechnology sector that can assist in global efforts to combat infectious diseases in Russia and abroad. To this end, Russia needs a strong innovation system from basic molecular biology through applied research and development, intellectual property and regulatory systems, scale-up and production capabilities, and commercial manufacturing, marketing and product distribution systems.

The Russian government recognizes that there is a clear need for stronger high-tech venture capital institutions to support many industrial sectors. The government has invested a few million dollars into several quasi-public institutions and has plans to expand these efforts. There has been limited success but little, if any, in the biotechnology field. In any case, this responsibility must be assumed by the private sector as soon as possible.

As already discussed, producing biotechnology items for the Russian market is not a simple task, even for the most experienced business entrepreneurs. Manufacturing products in Russia for export will be even more difficult. In addition to the complexities unique to biotechnology from clinical trials, to patent uncertainties, to potential military applications of civilian products, many problems hamper all types of businesses in the country. They include difficulties in finding secure facilities, the large number of repetitive inspections of premises and their contents, and the need for entrepreneurs to constantly search for financing in a country where commercial banks are accustomed to repayments of loans within six months. Inconsistent tax policies, intellectual property rights that do not reward scientific success and are rarely enforced, and complicated procedures for licensing facilities and approving products also inhibit commercial activity in Russia (see Appendix P for a key regulation concerning licensing). Finally, of special concern in the health sector is the perception of unfairness and lack of transparency associated with the procurement of drugs and medical devices and other types of fund transfers at the federal and regional levels.

Thus, the committee recommends that the Russian government intensify its efforts to develop a business environment that encourages investment in biotechnology activities. Even in the most favorable environments there are high rates of failure among new biotechnology firms and among new production processes established within existing firms. Therefore, rewards to investors for success should be substantial. Also, the government should recognize that many large enterprises owned or controlled by the government but on the path to privatization will have difficulty finding resources for updating facilities and for improving management and marketing practices to compete effectively. In some cases, government cost-sharing with such enterprises may be warranted during a transition period.

The committee also recommends that the Russian government promote investment in biotechnology niches that are particularly well suited for activities based in Russia. The manufacture of many types of pharmaceuticals and related products will remain beyond the competitive reach of Russian firms for the foreseeable future. However, there surely are market niches for Russian firms that have not been fully exploited.

One means of promoting investment is to support local production of selected items that are currently imported. For example, government procurement practices should ensure that high-quality, competitively priced Russian products are given adequate consideration when competing with better known imports. While adopting an import substitution policy for the long term might be counter-productive by creating an inward looking mentality among entrepreneurs, during the current economic transition period, it could be very important in starting new firms and in helping to ensure the viability of well-established firms.

A complementary approach is to support Russian manufacturers who are targeting markets in the countries of the former Soviet Union where longtime connections give Russian firms a considerable advantage over foreign firms trying to penetrate these markets. An obvious product for targeted marketing has been diagnostic test kits. Assessments of the needs and imports of these countries should reveal other opportunities as well, such as needs for vaccines and disinfectants.

Another market niche that seems well suited to Russian capabilities is the identification and testing of new natural antibiotic products, given the increasing reluctance of Western pharmaceutical firms to vigorously seek new classes of antibiotics. Russia has not been adequately explored for its microbial flora. The country may have novel micro-organisms in its vast territories.

In all of these areas, government officials and Russian researchers can play important supporting roles for private sector investors. By emphasizing quality control programs that encourage Russian manufacturers to adhere to international standards, the government could help Russian consumers gain confidence in products made in Russia.

In sum, the Russian government and the private sector face many challenges in the biotechnology sector. Special steps by the government are needed to support the emergence of a vibrant and sustainable base of biotechnology firms, and particularly those linked to research institutes, that will in time become internationally competitive. An optimistic approach is set forth in Box 4.3.

BOX 4.3
Developing the Animal Biotechnology Sector

"The optimal direction to advance the biotechnology industry is to prioritize the development of those aspects that are able to quickly become profitable and thereby attractive for private investors. Examples are cattle feeds and pet foods. Such activities could collectively become the 'locomotive' pulling the industry as a whole. This is possible because technologically and procedurally the industry is rather uniform, which allows human resources, skill sets, equipment, and procedures to 'spill over' from one branch of industry into another, first into those aspects of biotechnology whose products are sold to nongovernmental entities, particularly to individuals and for-profit companies."

SOURCE: Russian expert in agricultural biotechnology (October 2004).

5

Pillar Four:
The Human Resource Base

To be effective, the health, agricultural, and scientific infrastructures of any country must be built around capable and well-trained personnel. These professionals are called upon to perform diverse tasks such as identifying pathogens, engineering DNA, developing databases, reporting diseases, investigating epidemics and conducting epidemiological analyses, undertaking vaccination campaigns, inspecting restaurants and catering facilities, testing water systems, preparing patent applications, perfecting marketing tactics, and attracting venture capital. They also inform the public of health threats and recommend personal and community-based precautions during consultation sessions and through the media. But many complementary skills are also needed to safeguard public health.

In short, scientists are a key component, but not the only component, of the bioscience and biotechnology workforce; and the emphasis of this chapter is on scientists.

RETAINING SKILLED PROFESSIONALS

Soviet scientific and engineering capabilities were exceptionally strong. Indeed, the excellent undergraduate and graduate training at the university level was a tremendous asset during the Soviet era. Early in the post-Soviet transition, the Russian government had hoped to retain well-qualified professionals in their positions and to continue the tradition of high-quality education.

Yet with the economic decline in Russia and the widespread realization that sufficient salaries were essential to survive in a market economy, interest in science quickly declined, both among working scientists and among potential new entrants who were completing their training at the university level. Engineers often fared better financially than scientists because they could use their skills to address maintenance and other related practical problems facing the population. Also, they seldom encountered the types of regulatory issues that increasingly encumbered biomedical researchers and scientific entrepreneurs.

As shown in Figure 5.1, many Russian specialists and graduating students with skills relevant to infectious diseases have been changing their career tracks. Also, some of the best science students and young researchers have been relocating abroad. An indication of the total number of postgraduate students who have skills relevant to infectious diseases is shown in Table 5.1. The pool appears to be substantial. But the available statistics do not indicate the number of these students who are seeking shelter from the military draft or who are simply interested in the

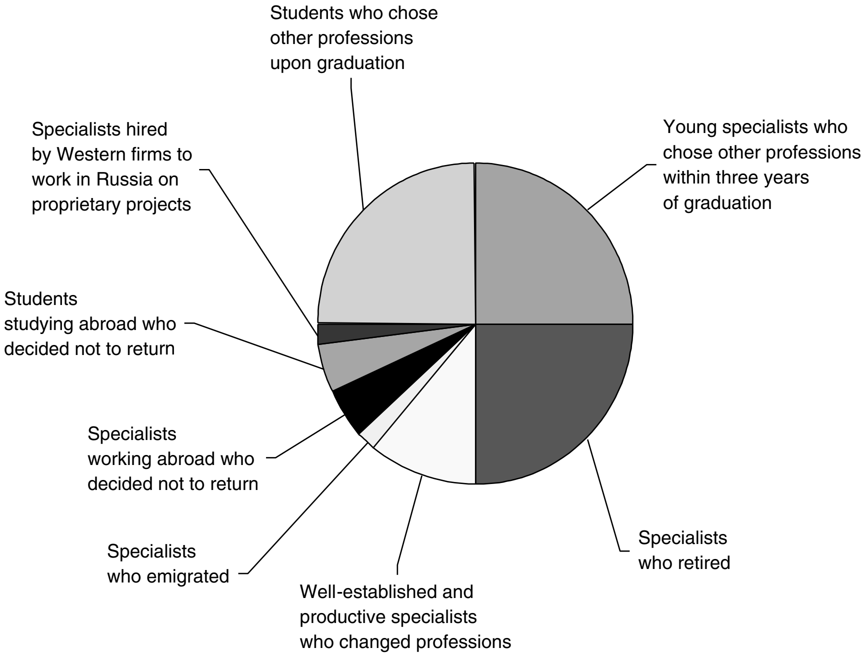


FIGURE 5.1 Loss of doctors, scientists, engineers, and students with skills relevant to infectious diseases who gave up their specialties in Russia in 2001.
NOTE: Estimates are based on available data published by the Russian government and on discussions with Russian authors of relevant statistical analyses, specialists of the Russian Academy of Sciences, and senior U.S. visa officials in Moscow. The annual loss of professionals and students has been estimated at 5,000 from a workforce of 100,000.
SOURCE: Adapted from Schweitzer, 2001. Reprinted with permission of Cameron Publications Services.

TABLE 5.1 Postgraduate Studies in Five Fields Relevant to Infectious Diseases: Russia, 1999-2001

	Enrollment			Entrants			Graduates		
	1999	2000	2001	1999	2000	2001	1999	2000	2001
Biology	4,955	5,589	5,917	1,674	1,913	2,006	1,119	1,354	1,338
Agriculture	3,074	3,118	3,219	1,001	1,116	1,160	755	834	814
Medicine	7,125	7,783	8,689	2,536	2,753	2,902	1,611	1,671	1,820
Pharmacy	224	234	255	75	78	97	49	59	51
Veterinary	918	954	998	331	324	344	173	213	237

SOURCE: Ministry of Industry, Science, and Technology, and Russian Academy of Sciences, 2003.

prestige associated with a scientific degree, motivations that are strong in Russia. Further, the statistics do not distinguish between the outflow of specialists from different disciplines. For example, there is anecdotal information that suggests molecular biologists are more likely to give up their professions than medical doctors who have greater opportunities to supplement their core incomes. In short, there is a serious problem in retaining a balanced and highly motivated scientific workforce.

At present, senior officials of the Russian government and leaders of the scientific community are greatly concerned about the "lost generation" of scientists and engineers. This is a result of declining interest in science during the early and mid-1990s, a decline which is still evident. The problem is particularly acute in the biological sciences.[1] For example, within the institutes of the Russian Academy of Medical Sciences, about 60 percent of researchers are over age 45; 25 percent are under 30; and only 15 percent are between 30 and 45. Research productivity of the older generation is gradually declining, and the younger generation is still developing its capabilities.[2] Thus, expectations for the overall effectiveness of the workforce have often been unrealistic, given the low proportion of those researchers who are in the prime of their careers.

The slow development of management skills relevant to the demands of a market economy in Russia has also become a perennial concern (see, for example, Zinov, 2003: 37). As noted in Chapter 4, successful entrepreneurship in the pharmaceutical/biotechnology sector is an important but scarce commodity. Many leaders of state-owned enterprises in the health and agricultural sectors have not adjusted well to the new market economy, and the number of successful directors of commercially viable small and medium-size enterprises associated with research institutes or operating independently is small.

[1]Interview with Deputy Minister for Industry, Science, and Technology, Moscow, June 2003.
[2]Data provided by Russian Academy of Medical Sciences, August 2003.

Realizing profit from commercial endeavors in the biotechnology sector is complicated, as discussed in Chapter 4. Legal and economic skills are often more important than scientific skills. Although the Russian government and foreign organizations have tried repeatedly to establish effective management training programs in Russia, the most successful training has frequently been on-the-job training offered by Western companies with facilities in Russia. As for managers of research institutes, the gap between their limited knowledge of the market economy and authoritative insights of their Western counterparts is significant. But much of the Western experience is not directly transferable to the Russian environment.

As for university-level technical training, Moscow State University, Sechenov Moscow Medical Academy, and Russian State Medical University are usually identified as the preeminent educational institutions for preparing future biomedical personnel. The Skryabin Academy for Veterinary Sciences and Biotechnology in Moscow is ranked highly for training new specialists to study animal diseases. In plant protection, there is no easily identifiable leading educational institute. Overall, Russia has more than 50 university-level institutions in the biomedical field and more than 30 veterinary schools associated with agricultural universities. Also, schools of pharmacy, plant protection, food safety, and other relevant disciplines are located in the more than 100 universities that include science and medical specialties. (An extensive listing of the relevant university-level institutions is contained in Buga et al., 1994).

For decades, university-level education has been linked to activities at research institutes because few universities have strong research capabilities. But only a small fraction of science students are able to take advantage of these links. For example, at the Skryabin Academy only a half-dozen of the 400 faculty members have active research programs that involve students. A handful of additional students spend time at research institutes, usually as graduate or postgraduate students. Overall, the very limited opportunities for students to participate in research activities should be expanded as the need is great. A representative of the department of the Russian Academy of Medical Sciences responsible for research on infectious diseases reported to the committee that about 30 postgraduate students are accepted at the 12 institutes of the department each year, but at the same time 10–20 junior scientists leave Russia each year after defending their dissertations at these same institutes. Thus the influx of new talent is small by any measure.

A NEW GENERATION OF SCIENTIFIC LEADERS

Against this background, the committee gives high priority to the nurturing of a new generation of young scientists and leaders in the basic and applied sciences and technologies who will be essential in the advancement of infectious disease prevention and control. To this end, **programs that encourage**

postdoctoral scientists to remain in Russia as practicing scientists through mentoring programs that prepare them for positions of scientific leadership deserve strong support.

As we have seen, the incentives for outstanding young scientists to abandon their scientific careers for more lucrative professions such as banking and trading, or to go abroad in search of better working conditions, are strong. The gaps they leave behind will continue to disrupt research activities long into the future. In the absence of new research, financial, and housing incentives for young scientists to continue to pursue scientific careers in Russia, the outflow will be extensive.

The Russian government has taken a positive step on a limited scale with a portion of federal research grants designated for support of young scientists. Modest success in attracting outstanding young scientists has been noted during the past several years, particularly in the prestigious field of biotechnology. However, while a few institutes with interesting and promising programs are able to attract talented graduates despite low salaries and difficult living conditions, most institutes are not as successful.

Another approach that might have a significant influence on the situation is for both Russian and Western governments to provide financial support for those institute directors prepared to use their own resources on a matching basis to improve working conditions and create long-term career trajectories. Such an approach would help ensure that young talented scientists, when recruited, would be placed in positions where they have strong opportunities to obtain permanent employment status. A related innovation would be to establish a program of reentry grants of sufficient size to encourage young scientists to return to Russia upon completion of training abroad.

As a second initiative, the committee recommends expansion of programs to continually advance the professional skills of specialists in fields related to infectious diseases, and particularly skills in addressing multidisciplinary challenges. Advanced training could be offered at leading research institutes in Moscow and in other major cities on a more systematic basis than has been the case in recent years. Of particular interest would be advanced training at the two model surveillance centers recommended in Chapter 2. Many Russian specialists have fallen behind in their professional skills simply because they have not had modern equipment or broadband access to information on the Internet. At other times, they have been isolated from international developments, and their skill levels have suffered accordingly. Opportunities for young Russian specialists to have hands-on training experiences at international centers in Europe and the United States could also be of considerable importance.

Important steps in these directions are already being undertaken by the Russian biomedical community, and they should be supported. For example, special courses organized by the Ministry of Health and Social Development provide opportunities for hospital physicians concerned about infectious diseases and other ailments to extend their specializations under the supervision of leading

Russian experts. International scientific schools and seminars in the biomedical sciences are organized annually in Russia. In addition, many collaborating centers of the World Health Organization in Russia offer refresher training for specialists in relevant fields.

Four other approaches beyond these two recommendations are also worthy of consideration: (1) placing postgraduates in Russian and international companies to help implement applied research projects under the joint supervision of their professors and senior company personnel; (2) initiating two-way exchange programs of mid-career scientists between research institutes and biotechnology companies; (3) providing specially-designed business training courses for research managers that reflect both Western experience and Russian realities; and (4) supporting professional organizations working in bioscience and biotechnology such as the Society of Epidemiologists, Microbiologists, and Parasitologists; the Society of Virologists; the Society of Biotechnologists; and the Union of Biotechnical Industry Enterprises.

Such approaches have occasionally been attempted in Russia. For example, the agriculture-oriented firm NARVAC employs outstanding students on a regular basis and works closely with educational institutions. This approach provides a privately owned research-oriented company as a home base for rising biotechnology leaders.[3]

Finally, there are also special needs for basic and advanced training in epidemiology, which is a rapidly developing field worldwide. Russian colleagues report that 4,306 epidemiologists, 515 parasitologists, 4,585 bacteriologists, and 239 virologists were conducting work related to epidemiology in Russia in 2000. In recent years, the workforce has been relatively stable, and these figures probably have not changed significantly (Onishchenko, 2002). Russian colleagues therefore suggest that Russia may have sufficient numbers of specialists in these fields and that the emphasis should be on training to ensure quality and effectiveness. It also seems appropriate for the specialists to be encouraged to impart their scientific expertise to local medical personnel as well.

In conclusion, Russian science and technology have much to offer the world as has been demonstrated in recent years. Attracting and retaining highly trained and well-motivated personnel are the central ingredients of Russia's expanded participation in international scientific activities and entry of its products into global markets. Yet as underscored previously, even if Russian scientists have concepts for new products, an entire team of factory managers and quality control specialists, accountants, and lawyers must lead the transformation of brilliant ideas into useful products. One way to promote this team concept might be to incorporate a component for improving the skills necessary to have more effective market-oriented teams into externally funded research and development projects.

[3]For additional approaches relevant to Russia, see OECD, 2001.

6

Reshaping U.S.-Russian Cooperation in the Biological Sciences and Biotechnology

Since the disintegration of the Soviet Union in 1991, a large number of U.S. and Russian organizations have actively promoted bilateral cooperation in the biological sciences and in biotechnology. Most bilateral activities have relied on the U.S. and Russian governments as funders and/or facilitators. Some programs have been oriented toward improving public health, agriculture, environmental protection, and biodefense in Russia and in the United States. Other programs have been directed toward the support of basic research. Most projects have been implemented by government organizations and by elite research and educational institutions in the two countries. In almost all cases, field and laboratory activities have been conducted in Russia with occasional visits by Russian specialists to the United States. Much of the funding for the Russian side, as well as for the U.S. side, has been obtained by the U.S. partners (see Appendix Q, which briefly describes some of the cooperative programs).

The U.S. government had until recently been Russia's most active international partner in promoting research related to infectious diseases. But recently, the World Bank and the Global Fund to Fight AIDS, Tuberculosis, and Malaria launched efforts in Russia directed at controlling HIV/AIDS and tuberculosis that are much larger than any U.S. initiatives. Other Western governments are also expanding programs directed at infectious diseases in Russia.

Thus, U.S.-Russian cooperation should be considered within the broader multilateral framework. In addition to the aforementioned international programs, the World Health Organization (WHO) and the Food and Agriculture Organization are playing increasingly active roles, both in providing assessments of disease incidence and trends, and in helping to coordinate the efforts of many governments. In particular, the WHO has for many years encouraged programs related to the control of infectious diseases and has established a number of infectious disease "collaborating centers" in Russia. The WHO will presumably continue to expand these efforts in the future.

EXPANSION OF BILATERAL COOPERATION

In the early 1990s, the U.S. and other Western governments began to support basic research in Russia, including research in the biological sciences. Several U.S. agencies such as the National Science Foundation, the National Institutes of Health, the National Aeronautics and Space Administration, and the Office of Naval Research were increasingly concerned that much of the world-class basic research capability of Russia would be lost because of the sharp decline in funding for science in the country.

Of special concern was the significant loss of talent accompanying the decline in Russian government support for research. As discussed in Chapter 5, this loss of talent has been primarily an *internal* movement of well-trained specialists away from science careers to the commercial sector in Russia. There has been a less dramatic, but nevertheless important, migration from Russian research laboratories to research centers in other countries.

Starting in 1994, the U.S. government initiated several nonproliferation programs that involved cooperative biological research activities. The programs were intended to help ensure that Russian expertise in biology and related fields relevant to weapons would not be transferred deliberately or inadvertently to countries or groups with intentions hostile to U.S. interests. More recently, related nonproliferation programs initiated by the U.S. government have improved safety and security procedures at Russian facilities where strains of dangerous pathogens are stored. These programs also have upgraded facilities for breeding research-quality rodents and for toxicological experiments with rodents and other small animals. Now refurbishing research and manufacturing facilities is underway so that they meet requirements for Good Laboratory Practices and Good Manufacturing Practices as called for by recently promulgated Russian regulations. In addition, biotechnology and the life sciences are clearly a priority area of interest to the International Science and Technology Center in Moscow (ISTC), an international program, which is sponsored by the U.S. and several other governments (see Figure 6.1).

The rapid spread of tuberculosis and HIV/AIDS in Russia has attracted considerable attention from the U.S. government, resulting in funding provided primarily by the U.S. Agency for International Development, which has a health, and not a nonproliferation, mandate (see Box 6.1). To address a number of other diseases as well, six U.S. departments have sizable programs to redirect former weapons expertise to public health, agriculture, and environmental problems within the framework of nonproliferation. The severe acute respiratory syndrome

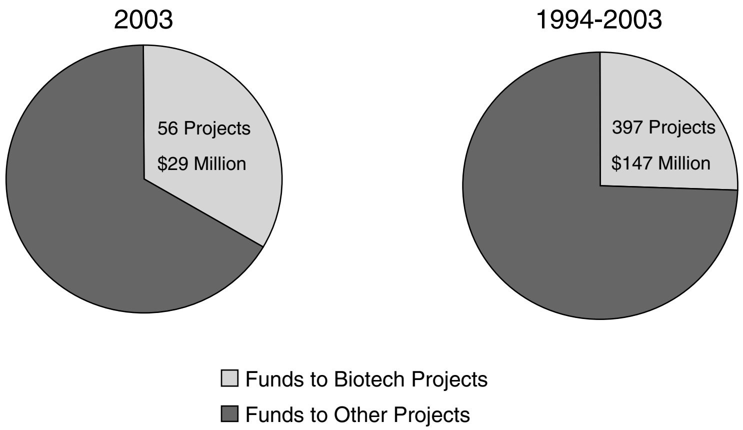


FIGURE 6.1 Projects funded by ISTC in Biotechnology and Life Sciences. SOURCE: ISTC Annual Report (2004).

(SARS) outbreak in 2003 made the two governments even more aware of the importance of cooperation in combating infectious diseases through both multilateral and bilateral channels (see Appendix R for a description of programs of special interest to Russia's Ministry of Health and Social Development).

In the non-governmental sector, several U.S. foundations, particularly the Howard Hughes Medical Institute and the Vishnevskaya-Rostropovich Foundation, have supported Russian biology researchers and institutions that contribute to world science, disease eradication in Russia, and higher education programs (see Box 6.2). In the commercial sector, a few U.S. pharmaceutical companies have established modest commercial relationships with emerging private sector firms and well-known research institutes. Some U.S. companies are investigating clinical trials of new drugs in Russia. However, investments by the private sector, particularly by U.S. industry, in Russian activities relevant to infectious diseases have been quite limited.

Overall, an impressive array of hundreds of bilateral projects in microbiology, virology, and other fields related to infectious diseases have been conducted over the past decade. The U.S. government currently budgets about $40 million annually for bilateral biological programs, with most of the funds provided for nonproliferation programs. As for industrial activities involving the biological sciences and biotechnology—such as the development and production of vaccines, drugs, and diagnostic devices and the introduction of genetically modified organisms—cooperative efforts have been limited, with U.S. private sector investors uncertain of the risks and skeptical of the rewards from financial involvement in Russia.

BOX 6.1
Examples of Activities in Russia Supported by U.S. Agency for International Development

Tuberculosis Prevention and Control

- Providing technical assistance, supported by World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC), which contributes to changes in diagnostics, treatment, surveillance, and case management practices in Orel, Ivanovo, and Vladimir
- Delivering drugs to the prison systems in selected oblasts
- Developing a treatment protocol for multi-drug-resistant tuberculosis

SOURCE: USAID (2003).

HIV/AIDS and Sexually Transmitted Disease Prevention

- Marketing campaigns for condoms launched in Samara and Saratov
- Training workshops and conferences, and upgraded laboratory equipment for the diagnosis of sexually transmitted diseases, provided by USAID together with CDC
- Increasing awareness of HIV/AIDS through radio, television, Internet, printed materials, concerts, and other youth-oriented activities

SOURCE: USAID (2003).

Additional programs

- Improving maternal and child health
- Increasing healthy life style and health awareness
- Increasing accessibility and quality of medical care

SOURCE: Ministry of Health (2003).

BOX 6.2
Vishnevskaya-Rostropovich Foundation

The Russian Federation health authorities consider the Children's Vaccination Initiative of the U.S.-based Vishnevskaya-Rostropovich Foundation a successful model for entering into international partnerships in the Russian public health domain. By focusing on the prevention of viral hepatitis B, the Foundation has demonstrated that it recognizes a major obstacle in the area of health that Russia now faces and has identified creative strategies for overcoming those obstacles. In the territories where adults and youth have been immunized by the Foundation, hepatitis B incidence rates have been reduced by 40–62%.

SOURCE: Ministry of Health (2003).

BOX 6.3
Realities of Visa Delays

In 2002, the CDC invited a young Russian specialist who had received a grant from the ISTC to participate in a training program on modern methods of RT-PCR analysis of sera samples. She applied for an American visa in March 2003 and traveled to Moscow for the required interview at the Embassy. Two months later, she was informed that her patronymic and first names had been switched in the document; and she started the process anew. In November, her ISTC grant expired, and she gave up. Then in February 2004, she unexpectedly was granted a visa. She immediately left for the United States since the validity of the visa could not be extended, even though there was no time to arrange for her to take along SERA samples [needed to maximize the benefits from her collaboration].

SOURCE: Russian research manager (October 2004).

Overshadowing these activities has been a stubborn legacy of mistrust from the Cold War, linked to U.S. allegations of covert biological weapons activities in Russia. This mistrust has permeated all levels of government in both countries, and has to some degree discouraged cooperation that might, on the one hand, expose sensitive information or, on the other hand, engender unwarranted concern about the intentions of former adversaries. That noted, mistrust over the possible misuse of biological research in the two countries may be gradually subsiding. However, suspicions still circulate among senior officials in both Moscow and Washington about the motivations of the other side for participating in cooperative programs. They sometimes allege that the failure of the other side to ensure complete transparency about their programs may be a screen hiding illicit activities. Unfortunately, mistrust has adversely affected bioengagement programs in many ways, including delaying visa issuances as illustrated in Box 6.3.

RECOMMENDATIONS FOR STRENGTHENING COOPERATIVE ACTIVITIES

Given the extensive financial and human resources already being devoted by the governments of the United States and Russia to bilateral efforts that address infectious diseases of global concern, the committee recommends three initiatives to improve the effectiveness of cooperation in bioscience and biotechnology to achieve both U.S. and Russian goals. The first initiative is of crucial importance and should be the centerpiece of a stronger, more sustainable, and more beneficial relationship between the two countries.

The U.S. and Russian governments should establish a bilateral U.S.–Russian intergovernmental commission on the prevention and control of infectious diseases. The commission would emphasize cooperative programs that address infectious diseases of global significance, and particularly diseases of special importance in Eurasia. The U.S.-Japan program, begun in 1965, could serve as a model for the commission. Subgroups of the commission might be established to consider the following topics: (1) epidemiology and surveillance of emerging human and animal diseases; (2) laboratory services, including detection, diagnosis, identification, and reference systems; (3) information systems and technologies; (4) biosafety and biosecurity; (5) advanced training; and (6) promotion of scientist-to-scientist contacts. Initially, financing of the activities that the commission endorses would have to come largely from the U.S. government. But a near-term goal should be for each side to cover its own costs during meetings and at the bench. An early task for the commission would be to consider recommendations presented in this report and the contributions of existing bilateral cooperative efforts in implementing the recommendations.

Once the work of the commission is under way, it may be desirable to identify diseases and research areas of priority concern. Panels of experts could then consider recent scientific findings and their relevance to the control of infectious diseases and to future research agendas. Further, annual scientific conferences could be organized. International organizations involving specialists from other countries and occasional workshops could also address approaches to facilitating cooperation. An important aspect of the commission's work would be to involve in its deliberations leading scientists as well as government administrators with budgetary responsibility who are in the position to reduce impediments to cooperation.

Finally, the U.S.-Japan program has been under way in this field for several decades. The program, jointly supported by both governments and involving multiple small, focused subgroups of experts has been helpful to both governments, especially in the area of infectious disease. The joint committee selects diseases and related topics based on their common relevance to public health in Japan and the United States or globally. The program's work has led to a better understanding of diseases and an improved capacity to prevent or treat them. In addition, the program provides an excellent opportunity for Japanese and U.S. scientists to collaborate and communicate with colleagues and build research relationships around the globe. A careful examination of how it operates could provide useful guidance in structuring a U.S.-Russian analog.

A second recommendation is to complete the integration of former Soviet biodefense facilities no longer involved in defense activities into the civilian research and production infrastructure of Russia. During the Soviet era, many biological research and production organizations participated in programs sponsored by the Ministry of Defense, in addition to research and production conducted by the ministry itself. The largest organization supporting bioweapons programs was the USSR Ministry of Medical and Microbiological Industry. Its several dozen facilities employed tens of thousands of technical personnel. After the collapse of the Soviet Union, these facilities (now affiliated with Biopreparat), along with many other biology-oriented facilities that had been dependent to a lesser extent on defense orders, encountered difficult economic conditions. Support from the Ministry of Defense declined dramatically. At most institutions that had been dependent on defense orders, such support was terminated completely.

While many other research and production facilities supported defense activities, almost all had civilian missions as well. Thus, during the 1990s the heavily-defense-oriented Biopreparat facilities presented the greatest challenge in bringing former defense scientists into mainstream civilian activities. Therefore, they are discussed in greater detail here.

Since 1991, almost all Biopreparat facilities have lost large portions of their personnel and have greatly slowed hiring of new technical personnel due to diminished government funding. In response, these facilities have turned to civilian-oriented research activities funded primarily by foreign sources. The manufacture of relatively simple products that can be sold in Russia and other countries of the former Soviet Union has also supplemented income and sustained a reduced level of operations. Yet they have had difficulty joining the Russian civilian infrastructure due to the hesitancy of civilian ministries to assume responsibility for their activities, a lack of historical ties with traditionally open institutes, and security concerns about details of past activities.

BOX 6.4
Themes for Collaborative Research on Countering Deliberate Misuse of Variola Virus: Areas of U.S.–Russian Cooperation in 2003

- New generation of smallpox vaccines
- Methods of emergency prevention and therapy of orthopox virus infections and postvaccination complications
- Immunobiological preparations for prevention and treatment of diseases caused by variola virus and other orthopox viruses, as well as for alleviation of post-vaccination complications
- Diagnostic kits for rapid species-specific identification of variola virus and other orthopox viruses
- Experimental models of smallpox for studying the efficacy of smallpox vaccines and anti-viral drugs
- Properties of variola virus and those of closely related orthopox viruses

SOURCE: U.S. Army Medical Research Institute for Infectious Diseases (October 2003).

BOX 6.5
An Alternative to Antibiotics

A team of Agricultural Research Service scientists and Russian researchers from the State Research Center for Applied Microbiology in Obolensk have developed bacteriocins, natural proteins produced by competing non-pathogenic bacteria, that destroy *Campylobacter* in the intestines of farmed birds, dramatically eliminating pathogens. Laboratory tests show that treated birds have *Campylobacter* populations millions or even billions of times lower than untreated ones. Food-borne bacterial infections, such as those caused by *Campylobacter*, are responsible for billions of dollars of economic losses in the United States and worldwide. Research results from this project have already resulted in patent applications and a Cooperative Research and Development Agreement with Cargill, Inc., and could provide an alternative to antibiotics in both the veterinary and medical fields.

SOURCE: U.S. Department of Agriculture (December 2004).

These Biopreparat facilities, however, have some of the strongest biological research capabilities in the country, particularly in dealing with dangerous pathogens. They have demonstrated, through international programs, that they can contribute significantly to both national and global efforts to combat infectious diseases (see, for example, Boxes 6.4 and 6.5). Thus, it is important that they be recognized as legitimate civilian research institutes and not be considered simply as employers of former bioweapons scientists who receive preferential treatment by foreign funders.

To implement the recommendation of further integrating former biodefense facilities into civilian research, it is important to increase the involvement of Russian specialists who did not participate in defense activities but who have important expertise related to disease prevention and control.

A sharp bifurcation of the Russian scientific community between former defense and non-defense scientists not only inhibits the exchange of information within Russia, but also results in a lack of adequate attention to the proliferation potential of the historically civilian biological research sector. Much research on dangerous pathogens conducted in facilities that were never associated with defense programs is inherently "dual-use," with potential military or terrorist applications. Young scientists with modern laboratory skills, direct access to biological materials, and strong financial ambitions could present a challenging concern.

The U.S. departments and agencies responsible for implementing nonproliferation programs often attempt to link former weapons researchers with civilian

BOX 6.6
Integrating Former Defense and Civilian Researchers

"Scientists with many years of experience working with the most dangerous pathogens can certainly create greater problems if they were to decide, or were forced, to use this experience elsewhere, say in countries governed by regimes with questionable track records. Their colleagues who worked at 'open' institutes usually have only general knowledge of Group A pathogens. Besides, weapon scientists possess specific skill sets and access to (dangerous) strains of micro-organisms. Both could be sources of *potential* threats, but in the case of weapon scientists, it is significantly higher to the point of becoming *realistic.* However, it is regrettable that ISTC requires a pre-determined ratio of weapon scientists for each project. The criterion should be the appraised degree of danger coming from the knowledge base of prospective project participants."

SOURCE: Former Soviet bioweapon scientist (November 2004).

researchers through subcontracting arrangements, and in some cases they have been quite successful. The basic problem remains, however. The U.S. government continues to focus its nonproliferation efforts on those scientists who had direct experience in the former Soviet defense program for reasons set forth in Box 6.6.

Greater efforts are needed to encourage Western program managers to recognize more fully that in the biological arena, the potential for supporting proliferation and terrorism does not only rest with former weapons scientists.

The third committee recommendation is for U.S. and other Western funders to establish true partnerships in Russia. Although some senior U.S. government officials have made efforts to discontinue the use of the term *assistance* when considering programs with Russia, the U.S. Congress, and U.S. government departments and agencies, along with the American public, perceive programs that involve transferring U.S. government funds to Russia as "assistance" regardless of the commonality of interests and the benefits to the United States. Additionally, notions of U.S. dominance in determining priorities for cooperation, in designing projects, and in working out the details of program implementation have often accompanied the term assistance. Such an approach does not foster sustainability when U.S. funding for joint programs diminishes. Thus, the adoption of the concept of *partnership* rather than *patronage* is long overdue. To this end, two approaches are proposed.

The first suggestion is to increase the role of Russian scientists and science administrators in designing cooperative programs and projects. U.S. financial support that requires U.S. programmatic control will not result in the best use of Russian resources. Russian organizations are usually more familiar with Russian capabilities than are U.S. organizations, enabling them to assume comparable responsibility for determining the priorities and details of cooperative programs. They are also capable of proposing the details of programs, and taking responsibility for successes and failures. Even though Russian managers find it difficult to estimate the economic benefit that will accrue from projects, or design realistic business plans, Western experts are seldom better equipped to do business in Russia. A genuinely cooperative effort in this area, therefore, is particularly crucial.

It is also important that Russians support cooperative programs with enthusiasm that transcends financial benefits. Once funding of a project terminates, an enthusiastic Russian partner is likely to search for ways to continue the activity or to expand upon it in future efforts. An example of a positive outcome of a cooperative project is set forth in Box 6.7.

At the same time, many examples exist of cooperative projects that were so poorly defined at the outset that results were compromised. Unfortunately, there are still research managers in Russia—and, indeed, throughout the world—whose primary interest is to receive money for projects without adequate interest in the contribution of the projects to scientific or economic advancement. Active American participation in projects is often useful in avoiding such difficulties.

A second, related, approach calls for increased Russian financial contributions to cooperative programs as a key to sustainability and as evidence that the programs reflect Russian national priorities. As an initial step, Western payment of salaries for Russian participants in cooperative programs should be gradually

BOX 6.7
Pushchino Animal Breeding Facility Awarded AAALAC Accreditation

In September 2004, the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC-International) awarded full accreditation to the SPF Animal Breeding Facility (ABF) of the Branch Institute of Bioorganic Chemistry of the Russian Academy of Sciences, Pushchino. Achievement of AAALAC accreditation is a key element of the ABF's business plan, developed one year ago (2003) through support from the BioIndustry Initiative, and will contribute to the development and sustainability of the ABF. Some of the benefits of AAALAC accreditation include: international recognition; inclusion in the AAALAC Directory and other publications; and access to new markets and clients.

SOURCE: BioIndustry Initative Newsletter, Department of State, Volume One (2004).

decreased and eventually phased out. In the long run, paying salaries is clearly a Russian responsibility. Western financial contributions could be directed more toward supporting institutional infrastructure needed for effective cooperation. Covering the costs of selected modern equipment and supplies and the costs of modern communications networks is increasingly important.

U.S. projects implemented through the ISTC highlight this issue. ISTC's approach favors support for salaries over support for non-salary items such as equipment, typically awarding less than 50 percent of the total amount to non-salary items in a given project. This is based on the belief that the provision of salary support is the most important factor in reducing incentives for the proliferation of expertise. This short-term argument is important, but it needs to be balanced against the longer-term viability of Russian institutes to continue operations after completion of individual projects. Whether or not there is external financing, the Russian government is usually compelled to provide at least minimal support for salaries whereas financing large equipment purchases is considered optional. As a result ISTC's best investment in many cases may be to spend 60 to 70 percent of project funds on equipment that will help sustain the research groups into the future. This approach has been successfully integrated into a related Department of State program, the BioIndustry Initiative. These and other shifts in the sharing of responsibility at the project level can often contribute to fostering genuine partnerships as well as helping to ensure the sustainability of cooperative activities.

Collectively, the recommendations in this report, and particularly those in this chapter, should help restore Russia's capacity to join with the United States and the broader international community in leading an expanded global effort to control infectious diseases. The proposed bilateral intergovernmental commission can play a pivotal role to this end.

Epilogue

Russia, with one-seventh of the world's land mass and a rich heritage of scientific achievements, has long had the unique experience and capability to help control the spread of infectious diseases. Now, globalization of travel and trade, emerging diseases, and the widening threat of bioterrorism have heightened the urgency of harnessing the scientific and technological abilities of all countries in a united counter-attack on pervasive and persistent disease agents that can wreak human and economic havoc. Clearly, Russia should be on the front lines of the global effort to prevent and contain outbreaks of disease, at home and abroad.

During the past decade, the United States and Russia have been engaged in a growing program of bilateral cooperation in bioscience and biotechnology. This cooperative effort was initiated to help reduce the likelihood that irresponsible governments or terrorists would gain access to and misuse expertise, technologies, or material from a weakened Russia that was in the midst of a dramatic economic transition. While making major contributions to achieving this objective, the joint program has also gained comparable importance in addressing human and agricultural diseases that directly affect the Russian population, and indeed populations in many countries.

As bilateral cooperation has evolved, the mistrust on both sides that had hampered scientific interactions in the biological sciences during the Cold War has diminished. Instrumental in this change were the many personal transoceanic relationships that now provide a solid foundation for expanded cooperative efforts. The importance of engagement activities is substantial in providing not only a scientific return but also mutual confidence in the legitimacy of research and related endeavors in bioscience and biotechnology of former adversaries.

This report proposes important steps toward rejuvenating Russia's capacity to contain endemic diseases and cope with newly emerging diseases. It underscores the fact that only the Russian government can chart a realistic course for ensuring the health and security of its population. But Russia's international partners, and particularly the United States, can play important supporting roles as outmoded concepts of assistance give way to true partnerships, as Russia increases its financial commitments to international efforts and Western countries become more engaged intellectually, and as Western partners move from bilateral to multilateral approaches in addressing problems that affect many countries.

Appendixes

Appendix A

Committee Biographies

David Franz, *Chair,* is chief biological scientist at the Midwest Research Institute. He served in the U.S. Army Medical Research and Materiel Command for 23 of his 27 years on active duty. Dr. Franz has served as both deputy commander and then commander of the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) and as deputy commander of the U.S. Army Medical Research and Materiel Command. Prior to joining the Command, he served as group veterinarian for the 10th Special Forces Group (Airborne). Dr. Franz served as chief inspector on three United Nations Special Commission biological warfare inspection missions to Iraq and as technical advisor on long-term monitoring missions. He also served as a member of the first two U.S./U.K. teams that visited Russia in support of the Trilateral Joint Statement on Biological Weapons and as a member of the Trilateral Experts Committee for biological weapons negotiations.

David Ashford is an epidemiologist with the National Center for Environmental Health (NCEH) at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. In this position, he coordinates branch epidemiological studies on public health preparedness against terrorism. He also acts as an NCEH contact point for biological terrorism preparedness, anthrax vaccine issues, and surveillance. Dr. Ashford received his DVM from Cornell University in 1986, and his Masters in Public Health and Doctorate in Science from Harvard University in 1989 and 1996 respectively. He is author of 60 articles related to zoonotic diseases and public health and 15 textbook chapters.

Carol Blair is a professor of microbiology at Colorado State University. Previously, Dr. Blair served as the assistant dean for biomedical sciences, associate dean for undergraduate education, and head of the microbiology department. Before joining the faculty at Colorado State University, Dr. Blair was a lecturer in microbiology at Trinity College in Dublin, Ireland, for five years. She received her Ph.D. in molecular biology from the University of California, Berkeley, and is a member of numerous scientific and academic associations, including: Phi Beta Kappa; Phi Kappa Phi; Sigma Xi; American Society for Microbiology; American Society for Virology (ASV); Society for General Microbiology; American Society of Tropical Medicine and Hygiene (ASTMH); and American Association for Advancement of Science (AAAS). Dr. Blair has served as a council member for the ASV and AAAS, and as chair of the American Committee on Arthropod-borne Viruses of the ASTMH.

Gail Cassell is vice president for scientific affairs, and distinguished Lilly research scholar for infectious disease at Eli Lilly and Company, Lilly Corporate Center. She has received a number of awards for her research in infectious diseases, including an honorary degree, and is a recent past president of the American Society of Microbiology. She has been active in national and international policy deliberations, including those of the National Institutes of Health (NIH) and the U.S.-Japan Cooperative Medical Science Program. She is also a member of the steering committee of the U.S.-Japan Cooperative Medical Sciences Program. She is a recent chair of the Board of Scientific Counselors of the National Center for Infectious Diseases of the CDC and a member of the Advisory Committee to the Director of CDC and the Director of NIH. She currently is a member of the Secretary of Health and Human Services Advisory Council for Public Health Preparedness. She is also a member of the Institute of Medicine (IOM).

Maurice Hilleman was director of Merck Institute and was formerly senior vice president of Merck Research Laboratories, West Point, Pennsylvania. He was also adjunct professor of pediatrics, University of Pennsylvania. His career included service in basic and applied agencies including the Department of Health and Human Services, World Health Organization (WHO), Overseas Medical Research Laboratory Committee of the Department of Defense, and special committees of the National Academies of Science and the Institute of Medicine. Dr. Hilleman was instrumental in the development of vital vaccines such as those for mumps and pandemic flu. In addition, he was very active in broader scientific work aimed at serving the international scientific community and giving back to society. Dr. Hilleman received his Ph.D. from the University of Chicago, held four honorary degrees, and was a member of the National Academies of Science (NAS) and the IOM. Dr. Hilleman remained involved in the process of producing this study until his death on April 11, 2005.

Christopher P. Howson is vice-president for global programs at the March of Dimes. Formerly, he was Director of the Board on International Health of the IOM. In his 12 years at the NAS/IOM, he directed 15 projects and in 1993 served as acting director of the IOM Medical Follow-up Agency. Before coming to NAS, he was senior epidemiologist at the American Health Foundation in New York City. He holds a Ph.D. in epidemiology from the University of California, Los Angeles.

Peter B. Jahrling is scientific adviser and senior research scientist at USAMRIID. He is head of the WHO collaborating center on arbovirus and hemorrhagic fever virus research at USAMRIID, and a member of the Committee on the Return of Biological Samples of the National Research Council, CDC/NIH guest editor for the 3rd and 4th editions of Biosafety in Microbiological and Biomedical Laboratories, and chairman of the Subcommittee on Laboratory Safety at the American Committee on Arthropod-borne Viruses.

Paul Keim is the Cowden Endowed Chair in Microbiology at Northern Arizona University and director of Pathogen Genomics at the Translational Genomics Research Institute (TGen). His current research interest includes genomic analysis of bacterial pathogens. His laboratory has developed high resolution strain typing analysis methods for *B. anthracis*, *Y. pestis*, and *F. tularensis*. Several collaborative projects are currently underway with scientists from the former Soviet Union to understand the ecology and epidemiology of these pathogens. He currently holds research funding from NIH, the Department of Homeland Security, the Federal Bureau of Investigation, and the National Science Foundation that supports a laboratory of about 40 researchers. He has served on grant review panels for the U.S. Department of Agriculture (USDA) and NIH. He has published 150 peer-reviewed journal articles. He is a Laboratory Affiliate at Los Alamos National Laboratory.

James LeDuc is the director of the Division of Viral and Rickettsial Diseases in the National Center for Infectious Diseases, CDC. His professional career began as a field biologist working with the Smithsonian Institution's African Mammal Project in West Africa. Following that he served for 23 years as an officer with the United States Army Medical Research and Development Command. He joined CDC in 1992 and was assigned to the WHO as a Medical Officer, later becoming the Associate Director for Global Health at the National Center for Infectious Diseases (NCID). His research interests include epidemiology of arboviruses and viral hemorrhagic fevers, and global health.

Matthew Meselson is Thomas Dudley Cabot Professor of Natural Sciences at Harvard University and co-director of the Harvard-Sussex program on chemical and biological warfare armament and arms limitation. He has conducted research mainly in the field of molecular genetics and is recipient of the NAS Award in Molecular Biology, the Eli Lilly Award in Microbiology, the Thomas Hunt Morgan Medal of the Genetics Society of America, and the Laskev Award for Special Achievement in Medical Science. He is a member of the Royal Society, the Academie des Sciences, the Russian Academy of Sciences, and the NAS. He has served as a consultant on chemical and biological weapons matters to U.S. government agencies.

Rebecca Morton is a professor in the department of veterinary pathobiology at Oklahoma State University (OSU). She is a diplomat of the American College of Veterinary Microbiologists and has served as head of the Microbiology Section of the Oklahoma Animal Disease Diagnostic Laboratory. She has twice received the OSU Regents Distinguished Award for the development and implementation of infectious disease courses for veterinary medical students. Her current research interest is tularemia and she is working with Baylor College of Medicine in the sequencing and annotation *Francisella tularensis* strains and the determination of virulence factors for vaccine development. She has also been active in screening drugs against biological threat agents and developing and testing of biosensors for the detection of biological agents.

Frederick A. Murphy is a professor at the School of Veterinary Medicine at the University of California, Davis. Formerly, he was dean of the school and earlier he was director of the NCID at CDC. He is a member of the IOM and of the NAS. He is a recipient of the Presidential Rank Award and is a member of the German Academy of Natural Sciences. He has been a leader in research on viral pathogenesis, viral characterization, and viral taxonomy; his interests include public health policy, comparative medicine, and new, emerging, and reemerging diseases.

Joseph Silva is dean of the School of Medicine at the University of California, Davis. Previously, Dr. Silva served as chair of the Internal Medicine Department. He received his MD from Northwestern University Medical School (Illinois). His internship and residency training were undertaken at Johns Hopkins Hospital and a fellowship in infectious diseases was completed at the University of Michigan Medical School. After serving two years in the U.S. Air Force, Silva returned to the University of Michigan, where he was appointed assistant professor of internal medicine in the division of infectious diseases before he joined UC Davis in 1983. He is a renowned clinician, with specialty and research interests in bacterial diseases. He is a physician who speaks Russian and has great credibility in infectious diseases that extends beyond those associated with biological weapons. He is on the Board of Regents of the American College of Physicians and was formerly governor of the Northern California Chapter.

Richard Witter is a collaborator at the USDA-Agricultural Research Service Avian Disease and Oncology Laboratory. His discoveries have contributed significantly to the control of Marek's disease, a virus-induced cancer of poultry, by vaccination. Marek's disease was the most costly poultry disease worldwide, and his achievements were the first example of practical control of neoplastic disease by vaccination. Dr. Witter is a member of the NAS.

Russ Zajtchuk is professor emeritus in the Department of Surgery at Rush University Hospitals. He is also Chief Executive Officer of Chicago Hospitals International, LLC. Dr. Zajtchuk received all his medical training at the University of Chicago. He spent 28 years in the U.S. Army; his last position in the army was as Commanding General of U.S. Army Medical Research and Materiel Command. Upon retirement from the army he spent five years at Rush University as Vice President for Advanced Technologies and International Health.

Appendix B

Organizations Consulted During the Study

VISITS IN RUSSIA[1]

Russian Governmental Organizations

Federal Agency for Health and Social Development (includes many responsibilities of former Ministry of Health)
Federal Service for Surveillance of Consumer Rights Protection and Social Welfare (includes State Sanitary Epidemiological Service of the former Ministry of Health)
Ministry of Education and Science (includes many of the departments of the former Ministry of Industry, Science, and Technology and the former Ministry of Education)
Ministry of Agriculture
Federal Veterinary Service
Ministry of Extreme Situations, Government of the City of Moscow
Center of the State Sanitary and Epidemiological Service in Moscow
Military Medical Academy of the Ministry of Defense, St. Petersburg
Pharmaceutical Committee

[1] Unless otherwise indicated, organizations are located in Moscow.

Private Companies

NARVAC Company
Biokad Company
Sistema: Medical Technological Holding Company
Elevar Company and Institute of Bioengineering Biokhimmash

Independent Organizations

TEMPO, Non-Commercial Partnership: Center of Modern Medical Technology
Association of Venture Capitalists, St. Petersburg

Academies

Russian Academy of Sciences
Russian Academy of Medical Sciences
Russian Academy of Agricultural Sciences

Research Institutions

Scientific Research Center of Toxicology and Hygienic Regulation of Biopreparations, Federal Medical Biological Agency (*Serpukhov*)
Central Scientific Research Institute of Epidemiology, Federal Service for Surveillance of Consumer Rights Protection and Social Welfare (*Moscow*)
Andzhaparidze Scientific Research Institute of Viral Preparations (*Moscow*)
State Research Center for Virology and Biotechnology "Vector" (*Koltsovo*)
State Research Center for Highly Pure Biopreparations (*St. Petersburg*)
Institute for Immunological Engineering (*Lyubuchany*)
State Research Center for Applied Microbiology (*Obolensk*)
M. M. Shemyakin and Yu. A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences (*Moscow*)
Engelhardt Institute of Molecular Biology, Russian Academy of Sciences (*Moscow*)
Institute of Cytology, Russian Academy of Sciences (*St. Petersburg*)
All-Russian Research Institute of Phytopathology, Russian Academy of Agricultural Sciences (*Golitsino*)
Ya. R. Kovalenko All-Russian Scientific Research Institute of Experimental Veterinary Sciences, Russian Academy of Agricultural Sciences (*Moscow*)
All-Russian Research Institute of Agricultural Biotechnology, Russian Academy of Agricultural Sciences (*Moscow*)

Educational Institutions

I. M. Sechenov Moscow Medical Academy
Moscow State University
St. Petersburg State University
K. I. Skryabin Moscow State Academy of Veterinary Medicine and Biotechnology

Other

Biopreparat
St. Petersburg Science Center of the Russian Academy of Sciences
International Science and Technology Center
U.S. Embassy
U.S. Agency for International Development
World Health Organization

CONSULTATIONS IN THE UNITED STATES

Department of Agriculture, Agricultural Research Service
Department of Defense, Defense Threat Reduction Agency
Department of Health and Human Services
Department of State, BioIndustry Initiative
Nuclear Threat Initiative
World Bank

Appendix C

Decision of the Board of the Ministry of Health of the Russian Federation: Tasks for the Periods 2001-2005 and 2006-2010

Decision of the Board of the Ministry of Health of the Russian Federation, March 20-21, 2001, on Progress in Implementing the Concept for Development of the Healthcare System and Medical Science: Tasks for the Periods 2001-2005 and 2006-2010

(EXCERPT FROM PROTOCOL NO. 6)[1]

The Board of the Ministry of Health of the Russian Federation notes that the past decade has been characterized by complex socioeconomic, political, and demographic changes in the country, which have altered the fundamental character of the activities of medical organizations and have raised a number of challenging new problems for the sector.

Negative changes affecting the status of public health and the need to adapt the existing healthcare system to real current conditions made it necessary to adopt a conceptual document to reflect the governing principles for further development of the healthcare system in Russia. Such a document was in fact produced in the form of the Concept for Development of the Healthcare System and Medical Science in the Russian Federation, which was approved by Government Resolution No. 1387 on November 5, 1997.

[1] Translated from the Russian by Kelly Robbins.

The Concept is aimed at maintaining and improving the health of the people and reducing direct and indirect losses to society by decreasing illness and mortality rates.

The first stage of fundamental measures to implement the Concept concluded in 2000. The majority of planned measures were carried out. This made it possible to ensure stable funding for healthcare institutions, improve the efficiency of resource utilization, and reduce the deficit in the Program of State Guarantees for Providing Free Medical Care to the Population.

In the aim of improving the system for healthcare standardization, metrology, and certification, the Russian Ministry of Health and the State Committee for Standardization and Metrology (Gosstandart) have created the Interagency Coordinating Council. A program for the development of patient management protocols is being implemented successfully, and another program has been approved for the training of specialists in the fundamentals of healthcare standardization.

Work has been initiated to standardize medical services and regulate the provision of medications, equipment, and other medical products to hospitals and clinics.

The introduction of new medical technologies, despite financial resource constraints, has substantially increased the volume of unique types of medical care delivered to the public. For example, the number of heart operations involving the use of artificial blood circulation has doubled, while the volume of aortic-coronary shunting operations has increased by a factor of 2.5. The number of patients on hemodialysis has doubled, kidney transplants are up by 50 percent, and marrow transplants have increased tenfold.

Measures to implement several federal targeted programs, including Urgent Measures to Fight Tuberculosis, Diabetes, Vaccine Prophylaxis, Anti-HIV/AIDS, and others, have been developed and approved and are currently being carried out.

In 2001, plans call for the adoption of targeted programs on arterial hypertension, oncology, and sexually transmitted diseases. Programs are also being worked out in the areas of child health and the development of the sanatorium and health resort sector. In 2002, a unified comprehensive program on preventing and combating diseases of a social nature will also be prepared.

Despite insufficient financing, the potential of the medical science sphere has been maintained successfully. In recent years, Russian scientists have developed new technologies for diagnosing and treating oncological diseases and surgical pathologies with the use of plasma streams, ultrasound, lasers, and photodynamic therapy. Active efforts are under way to use genetic engineering technologies in the treatment of a number of serious diseases.

. . .

Achievement of the strategic goals of state healthcare policy depends to a decisive extent on how well the healthcare system can be managed. In order to facilitate implementation of the Concept, the Ministry of Health has established a Council on Regional Policy and placed Health Ministry representatives in the various federal districts. The Ministry is creating district healthcare coordination councils and has reorganized itself to bring its structure into accord with the goals and objectives assigned to it by the government.

All of the aforementioned points make it possible to conclude that the Russian Ministry of Health and healthcare organizations of the various component entities of the Russian Federation have done a great deal of work within the Concept framework to maintain accessibility and volumes of healthcare services rendered to the population.

At the same time, despite the significant amount of work that has been done and financial resources that have been invested in healthcare, the necessary return has not yet been received and the measures that have been taken have not had an effective impact on public health indicators. Reform of the sector has been unacceptably slow. This situation urgently demands changes in basic objectives and approaches to the further development of healthcare in the country.

The Board has decided:

1. to deem it necessary to continue reshaping the healthcare system within the framework of Government Resolution No. 1387 of November 5, 1997, on Measures to Stabilize and Develop Healthcare and Medical Science in the Russian Federation and to set the following top priority objectives for the period up to 2010:

- reducing the rate of premature death (from cardiovascular diseases, accidents, injuries, poisonings, and malignant tumors)
- fighting diseases of particular significance with regard to the country's demographic situation (diseases threatening infants and maternal reproductive health as well as diseases affecting the elderly)
- fighting diseases representing a special threat to the health of the nation as a whole (tuberculosis, HIV/AIDS, drug addiction, alcoholism, sexually transmitted diseases)
- creating a real mechanism for providing resources for priority objectives in the development of the healthcare system
- developing disease prevention measures and a system for active health maintenance and restoration for the healthy population
- promoting an expanded understanding among the population of the value of health and a corresponding reflection of this understanding in people's behavior
- ensuring comprehensive development of medical science and cutting-edge medical and information technologies
- meeting the needs of the population in terms of medications and medical products
- shaping the medical-social insurance system
- determining price policy in the medical services market

- instituting a system of professional malpractice insurance and increasing the level of social protection afforded to medical personnel
- shaping the medical rehabilitation system and developing sanatorium- and health resort-based forms of treatment
- expanding organizational and legal forms of healthcare organizations and optimizing the nomenclature of medical specialties

SOURCE: Ministry of Health (2004c).

Appendix D

Main Goals and Objectives in Combating Infectious Diseases in the Russian Federation[1]

The main goals of health care agencies and institutions, as well as of the State Sanitary Epidemiological Surveillance Service of the Russian Federation, in the field of combating infectious diseases, are as follows:

- by 2010, eradicate measles within the framework of the measles eradication program
- keep diphtheria incidence at a sporadic level and prevent severe clinical forms of the disease and resulting mortality
- by 2010, reduce mumps and rubella rates to a level of not higher than 5 cases per 100,000 population and the whooping cough rate to no more than 10 cases per 100,000 population, and eradicate maternally-transmitted congenital rubella syndrome
- by 2010, reduce the viral hepatitis B rate to no more than 10 cases per 100,000 population and eradicate cases of infants becoming carriers
- implement organizational and practical measures within the framework of the global World Health Organization (WHO) program for polio eradication
- by 2010, reduce ascariasis rate by 80 percent within the framework of the WHO implementation strategy
- prevent incidence of localized cases of malaria
- within the framework of federal- and regional-level programs, stabilize the epidemiological situation with regard to socially conditioned infectious dis-

[1]Translated from the Russian by Supernova Translations.com.

eases (HIV/AIDS, other sexually transmitted diseases, tuberculosis) and reduce mortality and disability rates resulting from these diseases.

The main objectives of healthcare agencies and institutions, as well as of the State Sanitary Epidemiological Surveillance Service of the Russian Federation, in the field of combating infectious diseases are as follows:

- increase the effectiveness of the system of epidemiological monitoring of infectious diseases through universal use of computerized information analysis systems and monitoring of the environment, and through collective immunity of the population
- develop regulations and procedures regarding the prevention of infectious and parasitic diseases
- implement federal- and regional-level programs to ensure the sanitary and epidemiological wefare of the population
- within the framework of the national vaccination calendar, improve the vaccine-based prevention system for infectious diseases and achieve vaccination rates of more than 95 percent among children
- on the basis of the "Prevention of Nosocomial Infections" concept, develop regional programs and take organizational and practical steps for their implementation
- strengthen organizational measures to combat infections emanating from natural environment sources and, most importantly, ensure timely implementation of steps to reduce the reservoir population and number of carriers
- continuously monitor the spread of influenza viruses, ensure their timely delivery to the Federal Influenza Center of the Ministry of Health, and incorporate new strains of the viruses into influenza vaccines
- formulate a plan of activities to develop regulatory and procedural documentation and review existing sanitary rules and prepare new ones governing organizational, preventative, and epidemiological activities for specific nosological forms of infectious pathology
- increase the public awareness campaign to foster individual and collective compliance with infectious disease prevention measures
- take necessary steps to upgrade laboratories in treatment and prevention institutions, as well as in state sanitary epidemiological surveillance centers, outfit them with modern equipment, and introduce advanced methods of clinical detection of infectious disease agents (polymerase chain reaction, etc.)
- increase scientific research in the diagnosis, etiology, treatment, epidemiology, and prevention of infectious and parasitic diseases
- expand the scope of R&D activities in order to:
  — develop new rapid methods and means of clinical detection of infectious disease agents

— create vaccines for rubella and hemorrhagic fever with renal syndrome as well as a comprehensive meningococcal vaccine

— create new-generation vaccines, including live recombinant vaccines employing virus vectors produced using genetic engineering, live polyvalent antiviral vaccines, and DNA vaccines

— synthesize chemical substances and use them to develop new disinfectants, insecticides, acaricides, and repellents

— create technologies, equipment, and devices for sterilizing medical instruments and other hardware. In doing so, focus on products made of thermolabile materials and on new means of monitoring the effectiveness of disinfection and sterilization.

SOURCE: Onischchenko, G.G. 2002. Main Goals and Objectives in Combating Infectious Diseases in the Russian Federation. Epidemiological Situation and Basic Directions of Activities for Its Stabilization. All-Russian Congress of Epidemiologists, Microbiologists, and Parasitologists, Moscow, March 26-28. Ministry of Health, Moscow, 55-56. Reprinted with the permission of G.G. Onischchenko.

Appendix E

Regulations Regarding the Federal Service for the Supervision in the Sphere of Health and Social Development[1]

RESOLUTION
Of June 30, 2004, No. 323
Moscow

On approval of the Regulations regarding the Federal Service for Supervision in the Sphere of Health and Social Development.

(including amendments of August 12, 2004)

The Government of the Russian Federation hereby resolves:

1. To approve the attached Regulations regarding the Federal Service for Supervision in the Sphere of Health and Social Development.
2. That the Ministry of Health and Social Development of the Russian Federation shall submit to the Government of the Russian Federation, by October 1, 2004, draft normative legal acts for the purpose of repealing excessive powers provided by sub-paragraphs 6.8 and 6.9 of the Regulations regarding the Federal Service for Supervision in the Sphere of Health and Social Development.

Chairman of the Government of the Russian Federation M. Fradkov

[1]Translated from the Russian by Supernova Translations.com.

APPROVED
By Resolution of the Government
of the Russian Federation
on June 30, 2004, No. 323
(including amendments of August 12, 2004)

REGULATIONS
On the Federal Service for Supervision in the Sphere of Health and Social Development.

1. General provisions

1. The Federal Service for Supervision in the Sphere of Health and Social Development is a federal executive body which shall perform the functions of control and supervision in the sphere of Health and Social Development.
2. The Federal Service for Supervision in the Sphere of Health and Social Development shall be established under the Ministry of Health and Social Development of the Russian Federation.
3. The Federal Service for Supervision in the Sphere of Health and Social Development shall be guided in its activities by the Constitution of the of the Russian Federation, Federal Constitutional Laws, Federal Laws, normative legal acts issued by the President of the Russian Federation, normative legal acts issued by Ministry of Health and Social Development of the Russian Federation, and by these Regulations.
4. The Federal Service for Supervision in the Sphere of Health and Social Development shall carry out its activities directly, as well as through its territorial branches, and through interaction with other federal executive bodies, executive bodies of the Subjects of the Federation, local governments, public associations and other organizations.

2. Powers

5. The Federal Service for Supervision in the Sphere of Health and Social Development [henceforth "the Service"] shall have the following powers:

5.1. the Service shall:

5.1.1. supervise:

5.1.1.1. pharmaceutical activities;

5.1.1.2. in observance of state standards and technical specifications for products intended for medical use;

5.1.2. control and supervise the observance of state standards in social services;
5.1.3. control:
5.1.3.1. procedures for conducting medical examinations;
5.1.3.2. procedures for determining the extent of professional disability resulting from employment injury or occupational disease;
5.1.3.3. procedures for organizing and conducting medical examinations, as well as rehabilitation of the disabled;
5.1.3.4. performance of medico-legal and medico-psychiatric examinations;
5.1.3.5. production, manufacture, quality, effectiveness, safety, sale, and use of medications;
5.1.3.6. production, sale, and use of products intended for medical purposes;
5.1.3.7. preclinical and post-clinical research of medications, as well as observance of good laboratory and clinical practices;
5.1.3.8. observance of quality standards in rendering medical assistance;
5.2. the Service shall organize examinations of quality, effectiveness and safety of medications;

Pursuant to the Resolution of the Government of the Russian Federation of August 12, 2004 No. 412, paragraph 5.3 of these Regulations has been amended.

5.3. the Service shall issue:
5.3.1. licenses for conducting:

5.3.1.1. medical activities;
5.3.1.2. pharmaceutical activities;

See Order of The Federal Service for Supervision in the Sphere of Health and Social Development of July 13, 2004 No. 6-Pr/04 on the creation of the Central Commission of the Federal Service for Supervision in the Sphere of Health and Social Development for licensing of pharmaceutical activities.

5.3.1.3. activities relating to the provision of artificial limbs and orthopedic assistance;
5.3.1.4. activities relating to the production of medications, with the exception of medications intended for animals and medicated feed supplements;
5.3.1.5. activities relating to the production of medical equipment;
5.3.1.6. activities relating to the turnover of narcotic drugs and psychotropic substances (development, production, manufacture, processing, storage, transportation, measuring out, handling, distribution, pur-

chase, use, and disposal) included in List II pursuant to the Federal Law *On Narcotic Drugs and Psychotropic Substances*;

5.3.1.7. activities relating to the trade in psychotropic substances (development, production, manufacture, processing, storage, transportation, measuring out, handling, distribution, purchase, use, and disposal) included in List III pursuant to the Federal Law *On Narcotic Drugs and Psychotropic Substances*;

5.3.2. permits for:

5.3.2.1. use of new medical technologies;

5.3.2.2. import of medications (provided they are medications intended for medical purposes) to the territory of the Russian Federation in accordance with procedures established by the legislation of the Russian Federation;

5.3.2.3. export of medications (provided they are medications intended for medical purposes) from the territory of the Russian Federation in accordance with procedures established by the legislation of the Russian Federation;

5.3.2.4. import to the territory of the Russian Federation of unregistered medications for the purpose of conducting their clinical tests;

5.3.2.5. conducting clinical tests of medications;

5.4. the Service shall issue to organizations producing certificates of compliance for medications with the requirements set by the legislation of the Russian Federation in the process of licensing the production of medications;

Pursuant to the Letter of the Federal Service for Supervision in the Sphere of Health and Social Development of August 20, 2004 No. 2174/04, the system of state control of quality, effectiveness and safety of medications shall not envisage any mandatory forms of proof of conformity for medications outside of state control.

5.5 the Service shall register:

5.5.1. caps on selling prices of vitally important and essential medications in accordance with procedures established by the legislation of the Russian Federation;

5.5.2. medications and products intended for medical purposes;

5.6. the Service shall maintain:

5.6.1. a state register of medications;

5.6.2. a state register of vitally important and essential medications;

5.6.3. a list of health institutions which have the right to conduct clinical tests of medications;

5.7. the Service shall conduct performance reviews and certification of specialists dealing with medications;

5.8. the Service shall carry out, pursuant to established procedures, inspections of health institutions, drug stores, wholesalers of medications, social protection organizations, and other organizations and individual entrepreneurs engaged in the sphere of health and social protection of the population;

5.9. the Service shall perform the functions of the main agent for the disposal and receipt of Federal Budgetary funds earmarked for financing the maintenance of the Service and its operations aimed at achieving its statutory functions;

5.10. the Service shall, within its powers, protect information which constitutes a state secret;

5.11. the Service shall provide visiting hours for individuals, ensure timely consideration of their petitions, make decisions regarding these petitions and forward replies to petitioners within the time frames established by the legislation of the Russian Federation;

5.12. the Service shall ensure readiness of the Service for mobilization, and shall control and coordinate such readiness in all organizations under its supervision;

5.13. the Service shall conduct professional training of its staff, maintenance training, refresher courses and traineeship;

5.14. the Service shall, pursuant to the legislation of the Russian Federation, carry out the filing, storage, recording and use of archival documents resulting from the operations of the Service;

5.15. the Service shall, in accordance with the established procedure, maintain relations with government agencies in other countries and international organizations in the specified sphere of activity;

5.16. the Service shall, in accordance with the established procedure, conduct tenders and sign government contracts for the placement of orders for shipment of goods, performance of work, provision of services for the needs of the Service, as well as for scientific research and development intended to meet the needs of the State in the specified sphere of activity;

5.17. the Service shall perform other functions in the specified sphere of activity, provided such functions are envisaged by Federal laws, normative legal acts issued by the President of the Russian Federation or the Government of the Russian Federation;

6. The Federal Service for Supervision in the Sphere of Health and Social Development shall, for the purpose of exercising its powers in the specified sphere of activity, have the right to:

6.1 organize the necessary research, tests, examinations, analysis and estimates, as well as scientific research pertaining to carrying out supervision in the specified sphere of activity;

6.2. request and receive information necessary for decision-making on issues within the competence of the Service;

6.3. provide explanations to legal entities and physical persons on issues within the competence of the Service;

6.4. exercise control over the operations of territorial branches of the Service and organizations under its supervision;

6.5. attract, in accordance with the established procedure, scientific and other organizations, academics and specialists for joint work on issues pertaining to the specified sphere of activity;

6.6. obtain free access to any enterprise producing medications and obtain samples of the medications produced in accordance with the procedure established by the legislation of the Russian Federation;

6.7. make copies of documents necessary to control the production and quality of medications in accordance with the procedure established by the legislation of the Russian Federation;

6.8. ban production of medications and sale of stocks of already produced medications in cases listed in the Rules for the Organization of Production and Control of Quality of Medications, in accordance with the procedure established by the legislation of the Russian Federation;

6.9. ban advertisement of medications and appraise the advertiser of the necessity to amend the advertisement of a medication in cases envisaged by the legislation of the Russian Federation, in accordance with the procedure established by the legislation of the Russian Federation;

6.10. apply restrictive, preventive, and prophylactic measures envisaged by the legislation of the Russian Federation aimed at prevention and/or remediation of the consequences of a breach by legal entities or individuals of mandatory requirements in the specified sphere of activity, for the purpose of termination in instances of a breach of the legislation of the Russian Federation;

6.11. establish consultative and analytical bodies (councils, commissions, groups, colleges) in the specified sphere of activity;

7. The Federal Service for Supervision in the Sphere of Health and Social Development shall not have the right to carry out normative legal regulation in the specified sphere of activity, with the excep-

tion of the cases which shall be determined by Decrees of the President of the Russian Federation and Resolutions of the Government of the Russian Federation, nor shall it engage in the management of public property or in the provision of paid services;

The restriction of powers of the Service established in paragraph 1 of this provision shall not apply to the powers of the Head of the Service's Property Management Service which has been granted operational management powers, powers to resolve personnel issues and organize the operations of the Service.

III. Organization of Operations

8. The Head of the Federal Service for Supervision in the Sphere of Health and Social Development shall be appointed and dismissed by the Government of the Russian Federation on the recommendation by the Minister of Health and Social Development of the Russian Federation.

The Head of the Federal Service for Supervision in the Sphere of Health and Social Development shall be personally responsible for the performance of the functions and achievement of goals of the Service.

The Head of the Service shall have Deputies, appointed and dismissed by the Minister of Health and Social Development of the Russian Federation on the recommendation of the Head of the Service.

The number of Deputy Heads of the Service shall be determined by the Government of the Russian Federation.

9. The Head of the Federal Service for Supervision in the Sphere of Health and Social Development shall:

9.1. allocate the functions among his Deputies;
9.2. submit to the Minister of Health and Social Development of the Russian Federation:
9.2.1. draft regulations for the Service;
9.2.2. provide suggestions on caps for the number of employees and the wage bill for the headquarters and territorial branches of the Service;
9.2.3. provide suggestions for the appointment and dismissal of Deputy Heads of the Service;

9.2.4. provide suggestions for the appointment and dismissal of Heads of the territorial branches of the Service;

9.2.5. provide annual draft action plans and projected performance indicators for the Service, as well as annual plan execution reports;

9.2.6. provide suggestions for the Draft Federal Budget, insofar as they pertain to the financing of the Service;

9.3. appoint and dismiss personnel employed at the headquarters of the Service and Deputy Heads of its territorial branches;

9.4. address, in accordance with the legislation of the Russian Federation on the government service, issues pertaining to performing government service in The Federal Service for Supervision in the Sphere of Health and Social Development;

9.5. approve the administrative chart and job specifications for the headquarters of the Service within the limits of labor laws and the number of employees established by the Government of the Russian Federation, as well as budget expenditures for the headquarters of the Service within the appropriations approved for the relevant period in the Federal Budget;

9.6. approve the number of employees and wage bills for territorial branches of the Service within targets established by the Government of the Russian Federation, as well as budget expenditures for these territorial branches within the appropriations approved for the relevant period in the Federal Budget;

9.7 in accordance with, and pursuant to, the Constitution of the Russian Federation, Federal Constitutional Laws, Federal Laws, Acts issued by the President of the Russian Federation and Ministry of Health and Social Development of the Russian Federation, issue orders pertaining to issues within the competence of the Service.

10. Financing of expenditures of the headquarters and territorial branches of the Federal Service for Supervision in the Sphere of Health and Social Development shall be provided from the appropriations made for this purpose in the Federal Budget.

11. The Federal Service for Supervision in the Sphere of Health and Social Development shall be a legal entity and shall have a seal with the National Emblem of the Russian Federation and with its name, other seals, stamps, and letterheads of established form, as well as accounts to be opened in accordance with the legislation of the Russian Federation.

12. The location of the Federal Service for Supervision in the Sphere of Health and Social Development shall be in Moscow.

Appendix F

Recent Reports by the National Academies on Global Health Concerns

Learning from SARS: Preparing for the Next Disease Outbreak: Workshop Summary (2004)

Countering Agricultural Bioterrorism (2003)

Health Professions Education: A Bridge to Quality (2003)

Microbial Threats to Health: Emergence, Detection, and Response (2003)

The Resistance Phenomenon in Microbes and Infectious Disease Vectors: Implications for Human Health and Strategies for Containment: Workshop Summary (2003)

Who Will Keep the Public Healthy? Educating Public Health Professionals for the 21st Century (2003)

The Roles of Academic Health Centers in the 21st Century: A Workshop Summary (2002)

Emerging Infectious Diseases from the Global to the Local Perspective: Workshop Summary (2001)

Exploring the Map of Clinical Research for the Coming Decade: Symposium Summary, Clinical Roundtable, December 2000 (2001)

Informing the Future: Critical Issues in Health (2000)

Assessment of Future Scientific Needs for Live Variola Virus (1999)

The Pervasive Role of Science, Technology, and Health in Foreign Policy: Imperatives for the Department of State (1999)

Confronting AIDS: Update 1988 (1988)

Control of Cardiovascular Diseases in Developing Countries: Research, Development, and Institutional Strengthening (1998)

Pacific Partnerships for Health: Charting a New Course (1998)

America's Vital Interest in Global Health: Protecting Our People, Enhancing Our Economy, and Advancing Our International Interests (1997)

Controlling Dangerous Pathogens: A Blueprint for U.S.-Russian Cooperation, A Report to the Cooperative Threat Reduction Program of the U.S. Department of Defense (1997)

Conference on Human Health and Global Climate Change: Summary of the Proceedings (1996)

Global Health in Transition: A Synthesis: Perspectives from International Organizations (1996)

2020 Vision: Health in the 21st Century (1996)

Emerging Infections: Microbial Threats to Health (1992)

New Vaccine Development: Establishing Priorities; Volume II, Diseases of Importance in Developing Countries (1986)

Appendix G

Bioterrorism: A National and Global Threat[1]

(Excerpts)

A substantial share of Russian scientific and organizational measures to counter bioterrorism are being carried out in conjunction with the existing system for combating infectious diseases. The main objectives in this system are

- increasing the effectiveness of epidemiological monitoring of infectious diseases on the basis of comprehensive use of computerized information and analytical systems, environmental monitoring, and collective immunity of the population
- developing regulations and methodologies with regard to infectious disease prophylaxis
- implementing federal and regional programs to promote the sanitary-epidemiological welfare of the population
- improving the infectious disease vaccination system
- expanding the public information system for persuading the population to take personal and societal measures for infectious disease prophylaxis
- strengthening the material and technical infrastructure of laboratories in the treatment and prophylaxis institutions and centers of the State Sanitary Epidemiological Surveillance Service, providing them with the necessary equip-

[1] Translated from the Russian by Kelly Robbins.

ment, and introducing modern methods for detecting infectious disease pathogens (polymerase chain reaction, and others)

- stepping up scientific research in the area of diagnostics, epidemiology, treatment, and prophylaxis of infectious diseases.

SOURCE: Onishchenko, G.G., L.S. Sandakhchiev, S.V. Netesov, and R.A. Martynuk. 2003. Bioterrorism: A National and Global Threat. Vestnik Akademii Nauk [Herald of the Russian Academy of Sciences] 73, no. 3. (March):195-204 (in Russian). Reprinted with the permission of the Russian Academy of sciences.

Appendix H

Highest Priority Measures for Creating a System to Counter Biological Terrorism[1]

There have been numerous cases in which various countries have conducted research and technology programs that, while not formally violating the 1972 Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction, nevertheless give indications of clearly definite aims. These cases attest to the fact that this international agreement lacks sufficient restraining power, and they indirectly highlight the relative ease with which extremist groups and even lone terrorists could gain access to the basic active components in these types of weapons of mass destruction, namely infectious pathogens and toxins. Also of serious concern is the enormous number of facilities—more than a thousand worldwide—that maintain collections of pathogenic microorganisms and viruses.

Now quite common in the literature, the term "biological terrorism" and its synonyms essentially convey the concept of "microbiological terrorism." Let us also note in passing that, due to the lack of clarity on the meaning of infectious pathogens that has become firmly established in the general conceptual framework, certain authors equate them with toxins, although essentially and even terminologically the two represent fundamentally different categories of harmful agents.

People worldwide were shaken as a precedent was set for the wide use of infectious pathogens by the sending of contaminated materials through the mail in the United States and other countries in the last third of 2001. The leaders of world powers were forced to react to these incidents. Despite the fact that the

[1]Translated from the Russian by Kelly Robbins.

spectrum of reactions was very broad—from the emotionally exaggerated statement of George Bush regarding "ongoing biological warfare" to the adequate assessment of Vladimir Putin that "the use of biological agents for terrorist purposes has become a reality"—society was united in its opinion that the world had changed in the course of a few days and the twenty-first century had become qualitatively different. In our opinion, despite their seemingly "modest" scale, the 13 anthrax cases resulting from this malicious act, five of which were fatal, must be condemned by mankind just as strongly as previous instances in which weapons of mass destruction were used, such as the chlorine gas attacks during World War I and the atomic bombings of Japanese cities during World War II.

The reality of the use of infectious pathogens means we must decisively reject certain stereotypical opinions that have arisen not only among casual observers but also most unfortunately even in certain professional circles, namely that biological weapons problems are mythical and illusory in nature and may even have been dreamed up by military specialists for their own self-interested purposes. Biological terrorism is an enormous social evil, an extremely dangerous phenomenon carrying with it the threat of consequences that are difficult to predict yet intentionally unfavorable. Efforts to counter it will be effective only if they come in the form of a system of balanced and coordinated measures carried out at the federal, regional, and local levels. Of course, such measures must be scientifically based, technically feasible, and economically realistic. Here, the interests of effectively countering bioterrorism both as a global phenomenon and at the local incident level require careful and comprehensive scientific research and development work on a systemic basis, with the broadest possible international integration and the involvement of a large number of competent specialists. Understandably, the results of these systemic efforts will not be immediately evident; however, due to the extreme urgency of this problem, measures must be taken now, building on the basis of a thorough assessment of the current situation and aided by the knowledge and experience that have been accumulated in eliminating epidemic foci of especially dangerous infections and overcoming the consequences of other emergency situations. On this basis, we could already propose a number of measures that, if implemented, would facilitate progress in resolving the very complex problem of creating a bioterrorism prevention and response system.

In our view, this problem must primarily be resolved in conjunction with efforts to deal with two closely linked issues, namely the biological security of the country as a whole and the sanitary-epidemiological welfare of the population. Therefore, the following actions would be expedient:

- Assigning full authority and responsibility for leading and coordinating the bioterrorism-related efforts of various departments and agencies to those federal and local agencies responsible for overall biological security, with these agencies to include substantial representation from specialists from the State Sanitary Epidemiological Surveillance Service.

• Organizing or reestablishing on the basis of revised principles the activities of representative public organizations (problem-focused federal-level commissions, non-governmental scientific-technical coordinating councils of the Defense Ministry's Scientific Research Department), which previously set priorities and coordinated nationwide research and development efforts as well as the implementation of R&D results by industry.

It is of fundamental importance to develop a concept for the country's biological security during the first decades of the twenty-first century. This concept should define such crucial points as sources of biological danger; organizational principles for biological security; personnel and technical means for ensuring biological security; scientific-technical policy; top priorities for the development of the means and methods of protection; organizational, technical, and economic approaches to creating the necessary human and resource reserves; and so forth. The task of leading efforts to create this concept should understandably be assigned to the same federal agency that will be responsible for the country's biological security.

The biological security concept should also serve as a basis for the development of an orderly and well-focused policy on scientific research and development efforts on the above-mentioned related problems. Meanwhile, without waiting for the completion of the concept, a number of obviously useful measures could be taken aimed to improve the quality of products being created, reduce development costs, and speed the introduction in practice of new medical protection products derived from biological substances. Such measures could include the following:

• Conducting an expert review of all existing and planned programs of scientific research, testing, and design work aimed at creating products for medical use in the aim of using this work as the basis for a State Program for the Development and Industrial Production of Medical Protection Products for the Period up to 2010. This program must include only those products that have firm technical and economic foundations and are, if possible, dual-use in nature. This will promote the more efficient use of budgetary resources by eliminating duplication of orders by different agencies for the same product and ensuring the timely transfer of dual-use products from reserve to current production status.

• Designating the Main Military Medical Administration of the Russian Ministry of Defense as the single general state customer for medical protection products, with this agency to be responsible for compiling and submitting a government-wide order for the entire range of such products.

• Calculating the volume of stockpiles of medical protection products needed by the entire country and determining the procedures by which relevant agencies and departments will assemble, maintain, and continuously refresh their supplies.

• Clarifying and revising previously issued orders for specific types of domestically produced medical protection products and compiling a list of the names and amounts of products that must be imported from abroad.

• Evaluating the capacities of Russian industry and preparing proposals on including the following categories of medical protection products in long-range production plans:

— products previously developed and having the necessary technical and regulatory documentation that were never put into production

— products produced by enterprises in the other republics of the former Soviet Union that are now hard to obtain in the Russian Federation

— products in current demand that had to be removed from production for financial, technical, or other reasons

• Reorganizing licensing system activities conducted by the various committees under the Russian Ministry of Health (those on pharmacology; pharmacopeia; medical and immunobiological preparations; disinfectants, perfumes, and cosmetics; and new medical equipment and devices) as well as their operational affiliates (the Scientific Research Institute of Pharmacology, the L.A. Tarasevich State Institute of Standardization and Control of Medical Biological Preparations, the Scientific Research Institute of Disinfection Science, the Scientific Research and Testing Institute of Medical Equipment) in reviewing data on new medical protection products and programs for testing them at all stages of development.

A number of measures merit special discussion. Of exceptional importance in ensuring biological security, countering bioterrorism, and promoting the sanitary-epidemiological welfare of the population is the matter of organizing a nationwide unified automated system for biological monitoring. Scientific research institutes in the microbiological and epidemiological fields, State Sanitary Epidemiological Surveillance Centers, and other practical sanitary-epidemiological and veterinary institutions of the Russian Ministry of Defense, Ministry of Health, and Ministry of Agricultural Production could serve as the basis for such a system.

A significant set of measures of a legal and organizational-technical nature should also be implemented immediately. A central focus of such measures should be the strengthening of Russian legislation providing criminal penalties appropriate to the most serious crimes against humanity with regard to unauthorized actions involving the acquisition (isolation), storage, accumulation, or use for inhumane purposes of infectious human, plant, and animal pathogens presenting a potential or likely threat to human life or health. The following actions are also necessary:

- standardizing and strengthening the system of requirements for ensuring security at facilities involved in the isolation, storage, accumulation, scientific study, etc., of infectious human, animal, and plant pathogens
- minimizing the number of facilities (especially in major population centers) that are permitted to store Group 1 or Group 2 pathogens and selecting the best staffed and equipped institutions in the various regions to serve as interagency centers for the storage of such infectious agents
- giving these interagency centers federal priority status, providing them with armed guard services, instituting the appropriate access pass control regime, equipping their grounds with hard-to-overcome barriers with electronic alarm systems, and installing automatic intrusion and fire alarm systems in buildings where pathogen collections are housed
- requiring these federal priority status institutions to work with local and regional law enforcement and internal affairs agencies to develop antiterrorism security plans and adopt appropriate operating practices accordingly
- eliminating and preventing the future creation and augmentation of so-called "personal" collections of Group 1 and Group 2 pathogenic microorganisms and viruses, collections that are currently poorly controlled

Personnel training matters also require immediate attention inasmuch as inadequate understanding of biological weapons problems in the 1980s and 1990s led to practically the complete disappearance from training program curricula of topics related to protection against biological weapons, the microbiology of infectious pathogens, epidemiology, pathogenesis, clinical aspects, and the prevention and treatment of related infectious diseases. As a result, this led to a reduction in the average level of preparedness of specialists to take action in case of an emergency. This situation must be rectified without delay by reviewing relevant training programs and instituting new revised curricula for the training of medical personnel in all categories and specializations, especially epidemiologists, microbiologists, virologists, laboratory medicine specialists, and infectious disease specialists.

Of course, these top priority measures recommended for implementation do not touch on all aspects involved in countering bioterrorism in all its diverse forms. In our opinion, however, they will represent real steps toward resolving related problems associated with ensuring the biological security of the country and the sanitary-epidemiological welfare of the population.

SOURCE: K. K. Raevsky. Military Medical Academy. 2002. Highest Priority Measures for Creating a System to Counter Biological Terrorism. Military Prevention Medicine: Problems and Perspectives. Proceedings of the First Congress on Military Medical Prevention Programs in the Armed Forces of the Russian Federation. St. Petersburg (in Russian):75-77. Reprinted with the permission of the Military Medical Academy of the Russian Federation.

Appendix I

National Immunization Calendar of the Russian Federation

Age	Infections
Newborns (0 – 12 hours after birth)	Viral Hepatitis B (1st vaccination)
Newborns (3 – 7 days)	Tuberculosis (vaccination)
1 month	Viral Hepatitis B (2nd vaccination)
3 months	Diptheria, Pertussis, Tetanus, Polio (1st vaccination)
4.5 months	Diptheria, Pertussis, Tetanus, Polio (2nd vaccination)
6 months	Diptheria, Pertussis, Tetanus, Polio (3rd vaccination) Viral Hepatitis B (3rd vaccination)
12 months	Measles, Rubella, Mumps (vaccination)
18 months	Diptheria, Pertussis, Tetanus, Polio (1st revaccination)
20 months	Polio (2nd revaccination
6 years	Measles, Rubella, Mumps (revaccination)
7 years	Diptheria, Tetanus (2nd revaccination) Tuberculosis (1st revaccination)
13 years	Rubella (vaccination for girls) Viral Hepatitis B (vaccination)
14 years	Diptheria, Tetanus (3rd revaccination) Tuberculosis (2nd revaccination)
Adults	Diptheria, Tetanus (revaccination every 10 years after the last revaccination)

Comments:

1. National Calendar Immunizations can be provided by domestically and internationally produced vaccines that are registered and have obtained permission for use by approved order.
2. For newborns whose mothers are HbsAg carriers or hepatitis B patients at the third trimester of pregnancy immunization against viral hepatitis B is carried out by the scheme "0-1-2-12 months."
3. Vaccination against viral hepatitis B at the age of 13 is for those who were not immunized earlier.
4. Vaccination against rubella is carried out at the age of 13 for girls who were not immunized earlier or received only one vaccination.
5. Revaccination against tuberculosis is for children who are not infected with tuberculosis.
6. Revaccination against tuberculosis at the age of 14 is carried out for children who are not infected with tuberculosis and didn't receive immunization at the age of 7.
7. Vaccines used in accordance with the National Immunization Calendar can be injected simultaneously with various syringes in various places on the body.

Two Key Challenges in National Calendar Implementation:

1. Lack of hepatitis B vaccines in practice. At the first stage of the immunization program in the Russian Federation alone, demand could reach $50 million and Russian Federation Health authorities (both federal and local) are capable of providing not more than $20 million. This is the reason for restricting vaccinations against hepatitis B to risk groups of the population (such as for newborns whose mothers are HbsAg carriers, infants from orphanages, children with family members who are HbsAg carriers, adolescents between the ages of 11 and 17). All others must be vaccinated at their own expense, or at the expense of local budgets, insurance companies, enterprises, etc.
2. The absence of locally-produced vaccines against rubella, as well as combined MMR preparations. Newer vaccines, such as those for *Haemophilus influenzae* type b (Hib), *Herpes zoster* have existed for years, but are not incorporated into RF immunization programs. Thus children born every year will not be adequately protected against vaccine-preventable diseases.

SOURCE: Ministry of Health and Social Development, provided fall 2004.

Appendix J

Selected Russian Research and Related Institutions with Activities Relevant to Infectious Diseases, Diagnostics, Treatment, Prevention, and Control

I. Institutions Affiliated with the Ministry of Health and Social Development[1]

A. Federal Service for Surveillance of Consumer Rights Protection and Social Welfare

1. Astrakhan Branch of the Central Research Institute of Epidemiology (*Astrakhan*)
2. Central Scientific-Research Institute of Epidemiology (*Moscow*)
3. Martsinovskiy Institute of Medical Parasitology and Tropical Medicine (*Moscow*)
4. Kazan Institute of Epidemiology and Microbiology (*Kazan*)
5. Khabarovsk Institute of Epidemiology and Microbiology (*Khabarovsk*)
6. Gabrichevsky Moscow Scientific-Research Institute of Epidemiology and Microbiology and Garichevsky State Unitary Enterprise of the Moscow Scientific-Research Institute of Epidemiology and Microbiology (*Moscow*)
7. Nizhny Novgorod Institute of Epidemiology and Microbiology (*Nizhny Novgorod*)
8. Novosibirsk Scientific-Research Institute of Tuberculosis (*Novosibirsk*)
9. Omsk Scientific-Research Insitute of Natural Foci Infections (*Omsk*)

[1]Source: Ministry of Health and Social Development, Fall 2004.

10. Rostov Scientific-Research Institute of Microbiology and Parasitology (*Rostov-on-Don*)
11. Scientific-Research Institute of Disinfectology (*Moscow*)
12. Scientific-Research Institute of Leprosy (*Astrakhan*)
13. Scientific-Research Institute of Phtisiopulmonolgy (unit of the Sechenov Moscow Medical Academy) (*Moscow*)
14. State Scientific Center of the Russian Federation – Institute of Immunology (*Moscow*)
15. State Scientific-Research Institute of Medical Biological Products (*Moscow*)
16. Tarasevich State Scientific-Research Institute for Standardization and Inspection of Medical and Biological Preparations (*Moscow*)
17. St. Petersburg Pasteur Institute of Epidemiology and Microbiology (*St. Petersburg*)
18. St. Petersburg Scientific-Research Institute of Children's Infections (*St. Petersburg*)
19. St. Petersburg Scientific-Research Institute of Phtisiopulmonology (*St. Petersburg*)
20. Tyumen Institute of Zonal Infectious Pathology (*Tyumen*)
21. Yekaterinburg Institute of Viral Infections (*Yekaterinburg*)
22. State Research Center for Virology and Biotechnology Vector (*Koltsovo*)
23. State Research Center for Applied Microbiology (*Obolensk*)

B. Anti-plague Institutes and Stations

1. Irkutsk Anti-Plague Institute of Siberia and the Far East (*Irkutsk*)
2. Rostov Anti-Plague Institute (*Rostov-on-Don*)
3. Scientific-Research Anti-Plague Institute "MIKROB" (*Saratov*)
4. Scientific-Research Anti-Plague Institute of the Caucasus and Caucasus Area (*Stavropol*)
5. Volgograd Anti-Plague Institute (*Volgograd*)
6. Altai Anti-Plague Station (*Barnaul*)
7. Astrakhan Anti-Plague Station (*Astrakhan*)
8. Central Anti-Plague Station (*Moscow*)
9. Chita Anti-Plague Station (*Chita*)
10. Dagestan Anti-Plague Station (*Makhachkala*)
11. Elista Anti-Plague Station (*Elista*)
12. Kabardino-Balkarskiya Anti-Plague Station (*Nalchik*)
13. Khabarovsk Anti-Plague Station (*Khabarovsk*)
14. Northwest Anti-Plague Station (*St. Petersburg*)
15. Novorossiysk Anti-Plague Station (*Novorossiysk*)

16. Primoriye Anti-Plague Station (*Vladivostok*)
17. Tyva Anti-Plague Station (*Kyzyl*)

C. Biopreparat Complex

1. Institute for Immunological Engineering (*Lyubchany*)
2. Institute for Bioengineering Biokhimmash (*Moscow*)
3. St. Petersburg Scientific-Research Institute of Vaccines and Sera (*St. Petersburg*)

D. Institutes of the Russian Academy of Medical Sciences

1. Central Scientific-Research Institute of Tuberculosis (*Moscow*)
2. Chumakov Institute of Polyomyelitis and Viral Encephalitis (*Moscow*)
3. Scientific-Research Institute of Antibiotics (*Moscow*)
4. Gamaleya Scientific-Research Institute of Epidemiology and Microbiology (*Moscow*)
5. Scientific-Research Institute of Epidemiology and Microbiology (unit of Medical Ecology Scientific Center of the Far-Siberian Scientific Center) (*Irkutsk*)
6. Scientific-Research Institute of Influenza (*St. Petersburg*)
7. Mechnikov Scientific Research Institute of Vaccines and Sera (*Moscow*)
8. Andzhaparidze Scientific-Research Institute of Viral Preparations (*Moscow*)
9. Ivanovskiy Scientific-Research Institute of Virology (*Moscow*)
10. St. Petersburg Institute of Bioregulation and Gerontology (*St. Petersburg*)
11. Vladivostok Scientific-Research Institute of Epidemiology and Microbiology (*Vladivostok*)

E. Federal Medical-Biological Agency

1. Scientific-Research Institute of Hygiene, Occupational Pathology and Human Ecology (*St. Petersburg*)
2. Scientific-Research Institute of Hygiene, Toxicology and Occupational Pathology (*Volgograd*)
3. Scientific-Research Institute of Immunology (*Moscow*)

4. Scientific-Research Center for Toxicology and Hygienic Regulation of Biopreparations (*Serpukhov, Moscow Region*)
5. Institute of Biological Instruments (*Moscow*)
6. State Research Center for Highly Pure Biopreparations (*St. Petersburg*)
7. Institute of Toxicology (*St. Petersburg*)

II. Institutes Affiliated with the Ministry of Agriculture

1. Institute of Biotechnology and Veterinary Medicine (*Moscow*)
2. All-Russia Research Institute of Animal Health (*Yurevets/Vladimir*)
3. All-Russia Scientific Research Institute for Control, Standardization, and Certification of Veterinary Products (*Moscow*)
4. All-Russia Research Institute of Plant Quarantine (*Moscow Province*)

III. Institutes of the Russian Academy of Agricultural Sciences

1. All-Russia Scientific Research Institute of Biological Plant Protection (*Krasnodar*)
2. Vavilov All-Russia Scientific Research Plant Breeding Institute (*St. Petersburg*)
3. All-Russia Scientific Research Institute of Phytopathology (*Golitsino*)
4. All-Russia Scientific Research Institute of Plant Protection (*Pushkin and Voronezh*)
5. Far East Scientific Research Institute of Plant Protection (*Primorskiy Territory*)
6. All-Russia Scientific Research Institute of Agricultural Biotechnology (*Moscow*)
7. Kovalenko All-Russia Scientific Research Institute of Experimental Veterinary Medicine (*Moscow*)
8. Skryabin All-Russia Research Institute of Helminthology (*Moscow*)
9. All-Russia Scientific Research Institute of Veterinary Virology and Microbiology (*Pokrov*)
10. All-Russia Scientific Research Institute of Pathology, Pharmacy, and Therapy (*Voronezh*)
11. All-Russia Research Institute of Veterinary Sanitation, Hygiene, and Ecology (*Moscow*)
12. All-Russia Research Veterinary Institute of Poultry Breeding (*Lomonosov*)
13. All-Russia Research and Technology Institute of Biological Industry (*Shchelkovo*)

IV. Institutes of the Russian Academy of Sciences

1. Engelhardt Institute of Molecular Biology (*Moscow*)
2. Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry (*Moscow*) (with branch in *Pushchino*)
3. Institute of Gene Biology (*Moscow*)
4. Institute of Microbiology (*Moscow*)
5. Institute of Molecular Genetics (*Moscow*)
6. Skryabin Institute of Biochemistry and Physiology of Microorganisms (*Moscow*)
7. Center of Bioengineering (*Moscow*)
8. Institute of Medical Biological Problems (*Moscow*) (SRC)
9. Institute of Parasitology (*Moscow*)
10. Sukachev Institute of Forestry Research (*Moscow*)
11. Institute of Cytology (*St. Petersburg*)
12. Institute of Biologically-Active Substances (*Chernogolovka*)
13. Institute of Biochemistry and Physiology of Plants and Microorganisms (*Pushchino*)
14. Institute of Protein Research (*Pushchino*)
15. Institute of Theoretical and Experimental Biophysics (*Pushchino*)
16. Institute of Cell Biophysics (*Pushchino*)
17. Institute of Fundamental Problems of Biology (*Pushchino*)
18. Institute of Biological Instrumentation (*Pushchino*)
19. Institute of Organic Chemistry (*Novosibirsk*)
20. K. A. Timiryazev Institute of Plant Physiology (*Moscow*)
21. Institute of Bioorganic Chemistry (*Novosibirsk*)
22. Institute of Cytology and Genetics (*Novosibirsk*)
23. Institute of Ecology of Plants and Animals (*Yekaterinburg*)
24. Institute of Ecology and Genetics of Microorganisms (*Yekaterinburg*)

V. Other Institutions of Special Interest

1. Institute of Molecular Diagnostics (*Moscow*)
2. Institute of Genetics and Selection of Microorganisms (*Moscow*)
3. Moscow State University (*Moscow*)
4. St. Petersburg State University (*St. Petersburg*)
5. Urals State University (*Yekaterinburg*)
6. Volgo-Vyatska State University (*Kirov*)
7. Academy of Medical Sciences (*Kirov*)
8. Scientific and Research and Design Institute Biotin (*Kirov*)

SRC: State Research Center

Appendix K

Scientific and Methodological Research Results Highlighted by the Russian Ministry of Health and Social Development[1]

Examples of Research Results Highlighted (Excerpts)

Basic and applied research has produced data on the following:

- The epidemiological significance of nontoxic strains of *Corynebacteria diphtheriae* that carry diphtheria toxin genes (G. N. Gabrichevsky Scientific-Research Institute of Epidemiology and Microbiology, Moscow, and the Pasteur Scientific Research Institute of Epidemiology and Microbiology, St. Petersburg).
- The role of a deficit of isotypes of human complement component C4, attesting to a predisposition to develop such diseases as gastric ulcer, glaucoma, or chlamydiosis (G. N. Gabrichevsky Scientific-Research Institute of Epidemiology and Microbiology, Moscow).
- The variability and genetic drift of the measles virus (G. N. Gabrichevsky Scientific-Research Institute of Epidemiology and Microbiology, Moscow).
- Immunopathological mechanisms of the development of helicobacterial infection and its connection with destructive gastrointestinal pathology (Pasteur Scientific-Research Institute of Epidemiology and Microbiology, St. Petersburg).
- The formation of the dominant mycobacterial group—the Beijing family—detected by the genetic marking method (Pasteur Scientific-Research Institute of Epidemiology and Microbiology, St. Petersburg).

[1]Translated from the Russian by Kelly Robbins.

Methods have been developed for assessing the intensity of local and systemic immunity to *Corynebacteria diphtheriae*. Based on diphtheria infection models, a set of immunity status analysis methods has been developed for the first time, making it possible to evaluate the intensity of antibacterial and antitoxic immunity (I. N. Blokhina Scientific-Research Institute of Epidemiology and Microbiology, Nizhny Novgorod).

Researchers have discovered certain features of the genetic characteristics of HIV-1 strains circulating among risk groups. It was shown that one strain of HIV-1 caused more than 80 percent of all cases of HIV infection in Russia. Three recombinant varieties of HIV-1 were found in Russia—A/E, D/G, and A/G—which attests to the substantial contribution of such viruses to the epidemiological process of HIV infection in our country. Based on these research results, nucleotide sequences obtained from 250 new varieties of HIV-1 have been deposited in the International Gene Bank (GenBank). Another result of this work was the application in specific epidemiological research studies of molecular-epidemiological methods based on the genetic characterization of HIV-1 varieties (Russian Academy of Medical Sciences D. I. Ivanovsky Scientific Research Institute of Virology, Russian Academy of Medical Sciences O. G. Andzhaparidze Scientific-Research Institute of Viral Preparations, and various applied research institutes focusing on problems of diagnosing and preventing HIV infections and AIDS).

The effectiveness of using the phytopreparation Erakond to provide pregnant women with non-specific protection against herpetic and respiratory viruses has been demonstrated (Scientific-Research Institute of Viral Infections, Yekaterinburg).

Various types of test systems based on hybrids producing type 1 and 2 antibodies have been designed to detect antigens to the herpes simplex virus. Genetic methods have been developed for serogrouping, typing, and clonal analysis of meningococci (Russian Academy of Medical Sciences O. G. Andzhaparidze Scientific-Research Institute of Viral Preparations, Moscow).

In conjunction with efforts to improve the epidemiological monitoring system, the following accomplishments have been made:

- A system for unified epidemiological monitoring of measles and rubella has been developed, and further research has been done to document its scientific foundations (G. N. Gabrichevsky Scientific-Research Institute of Epidemiology and Microbiology, Moscow).
- Two types of recombinant protein-based immunoenzyme systems have been designed to determine specific IgG and IgM antibodies to the rubella virus. A seroepidemiological study has been conducted regarding postinfection and postvaccination immunity to the rubella virus among various groups in the population (Russian Academy of Medical Sciences O. G. Andzhaparidze Scientific-Research Institute of Viral Preparations, Moscow).

• Improvements have been made in the system for epizootic monitoring in Siberian plague foci, as well as in the tactics and methods for studying natural Siberian plague foci (Scientific-Research Anti-Plague Institute, Irkutsk).

Following is a list of achievements in the development of new preparations and methods for diagnosis, immunoprophylaxis, and immunotherapy:

• The growth medium for the culture of the diphtheria pathogen has been improved, and a new means of preserving and transporting diphtheria strains has been developed, along with an accelerated method for detecting the presence of the diphtheria toxin gene (G. N. Gabrichevsky Scientific-Research Institute of Epidemiology and Microbiology, Moscow).
• Work has continued with the aim of creating five new Russian vaccines and evaluating their effectiveness (G. N. Gabrichevsky Scientific-Research Institute of Epidemiology and Microbiology, Moscow, and Russian Ministry of Health Central Scientific-Research Institute of Epidemiology, Moscow).
• A concentrated leptospirosis vaccine has been introduced in practice (Scientific-Research Institute of Medical Preparations, Rostov).
• Two original new substances (synthetic hexapeptides) and the preparation Phosphazide have been synthesized (Russian Ministry of Health Central Scientific-Research Institute of Epidemiology, Moscow).
• An immunoenzyme test system has been developed for the quantitative and qualitative determination of human complement component C4 (Russian Ministry of Health Central Scientific-Research Institute of Epidemiology, Moscow, and G. N. Gabrichevsky Scientific-Research Institute of Epidemiology and Microbiology, Moscow).
• Based on a test system for determining the functional activity of C4 component, a method has been developed for assessing the targeted inhibition of binding of one complement subcomponent (G. N. Gabrichevsky Scientific-Research Institute of Epidemiology and Microbiology, Moscow).
• Immunoenzyme methods have been developed for the quantitative determination of serum IgG, IgA, and IgM, and monospecific polyclonal antisera for IgG 1, IgG2, IgG3, and IgG4 have been obtained (G. N. Gabrichevsky Scientific-Research Institute of Epidemiology and Microbiology, Moscow).
• Immunoenzume test systems have been developed for serodiagnosis of viral hepatitis C, detection of *Coxiella burnetii* antigens, and diagnosis of *H. pylori* infection (Pasteur Scientific-Research Institute of Epidemiology and Microbiology, St. Petersburg).
• Test systems have been created for the diagnosis of meningitis caused by enteroviruses, herpes group viruses, and flavovirus (Russian Ministry of Health Central Scientific-Research Institute of Epidemiology, Moscow).
• A test system has been developed to detect antibodies to cytomegalovirus (CMV-Screen), herpes simplex virus, measles, and mumps (Russian Academy of

Medical Sciences O. G. Andzhaparidze Scientific-Research Institute of Viral Preparations, Moscow).

- A set of documentation has been produced on a non-invasive immunoenzyme analytical test system for detecting toxocara antibodies in saliva (Ye. I. Martsinovsky Institute of Medical Parasitology and Tropical Medicine, Moscow) and for detecting opisthorchiasis antibodies and antigens in patients' bile (Scientific-Research Institute of Regional Infectious Pathology, Tyumen).

Test systems have been approved for the detection of DNA from toxic strains of *Corynebacterium diphtheriae* and from the hepatitis B virus. A pharmacopeia number has been obtained for test systems for detecting RNA from the hepatitis C and hepatitis D viruses, DNA from *Chlamydia trachomatis*, and human immunodeficiency virus. A pharmacopeia number has also been issued for a DNA-polymerase preparation from *Thermus aquaticus* (Russian Ministry of Health Central Scientific-Research Institute of Epidemiology, Moscow).

Laboratory diagnostics for hepatitis C have been improved (Russian Academy of Medical Sciences D. I. Ivanovsky Scientific-Research Institute of Virology, Moscow, and Russian Academy of Medical Sciences O. G. Andzhaparidze Scientific-Research Institute of Viral Preparations, Moscow).

State quality control testing has been completed on test systems for detecting DNA from cytomegalovirus, *Ureaplasma urealyticum*, and *Mycoplasma hominis*, and all these systems have been recommended for practical clinical use (Russian Ministry of Health Central Scientific-Research Institute of Epidemiology, Moscow).

A test system for the detection of mycobacteria tuberculosis DNA and another for the quantitative determination of immunodeficiency virus RNA are currently in the state testing stage (Russian Ministry of Health Central Scientific-Research Institute of Epidemiology, Moscow).

Following are objectives accomplished as part of efforts to improve the system of prophylactic and antiepidemic measures in accordance with regional specifics of infectious pathology:

- Data have been obtained on the evolution of the epidemic process for hepatitis A, B, and C in major cities (I. N. Blokhina Scientific-Research Institute of Epidemiology and Microbiology, Nizhny Novgorod).
- Materials from the Register of Opisthorchiasis Foci in Russia have been analyzed to identify resistant invasive foci (Scientific-Research Institute of Regional Infectious Pathology, Tyumen).
- An epidemiological forecast has been prepared with regard to meningococcal infection rates based on the identification of the most virulent and epidemically significant strains with the help of typing and clonal analysis of the infectious pathogen (Russian Ministry of Health Central Scientific-Research Institute of Epidemiology, Moscow) as well as seromonitoring (G. N. Gabrichevsky Scientific-Research Institute of Epidemiology and Microbiology, Moscow).

- A set of prophylactic and antiepidemic measures has been put into practice with the aim of preventing the spread of rotaviral infections among newborns and infants in the first months of life, who comprise a high-risk group for such infections (G. N. Gabrichevsky Scientific-Research Institute of Epidemiology and Microbiology, Moscow).
- Epidemiological and clinical aspects of yersinosis in natural foci in Eastern Siberia have been studied, along with bactericidal phagocytosis mechanisms of the pseudotuberculosis microbe with a varied assortment of plasmids (Scientific-Research Institute of Regional Infectious Pathology, Tyumen).
- Ten disinfectant preparations have been developed—bior-H, intercide, dezolon, dezoflan, okadez, deziskrab, Laina-bio, Neofos-Similar, and others—all of which are promising for the prophylaxis of various nosocomial infections (Scientific-Research Institute of Disinfection, Moscow).
- Six insecticide and repellent preparations have been developed, including fitar, neodikhlofos, biozashchita, and akromed, for protection against flying and non-flying insects (Scientific-Research Institute of Disinfection, Moscow).
- A study has been made regarding the imported preparation Baytex 40% and a selection of inexpensive Russian preparations, and an assessment has been made regarding their effectiveness in natural foci of tick-borne encephalitis, Lyme disease, and Crimean hemorrhagic fever (Scientific-Research Institute of Disinfection, Moscow).

SOURCE: Onishchenko, G. G. 2002. Scientific-Methodological Support for the Activities in the Prevention of Infectious and Parasitic Diseases. Epidemiological Situation in the Russian Federation and Basic Areas of Activity for Its Stabilization. All-Russian Congress of Epidemiologists, Microbiologists, and Parasitologists, Moscow, March 26-28, 2002. 53-55 (in Russian). Reprinted with the permission of G. G. Onishchenko.

Appendix L

List of Research Projects Proposed in Open Competitions Organized in 2003[1]

Title of Project	Financial Support (in rubles)
Genomic micromatrices for determining the link between *Helicobacter pylori* and early stomach cancer	3 million
Role of oxide-modified fibrinogen and lipoproteins in the development of cardiovascular diseases and their complications	1 million
Creation of new material based on spider web protein structures	2 million
Creation of transgenic plants to serve as superproducers of targeted proteins (including those for medical use)	3.5 million
Bioinformatic approaches in biotechnology	3 million
Synthesis of biogenic surfactants with a broad range of functional characteristics	1.5 million
Biosafety of ecosystems in the Russian Federation with regard to invasive exotic species	1.5 million
Development of food product technologies based on non-standard agricultural raw materials biotransformed with the aid of multistrains and enzyme systems	900,000

[1]The competition was sponsored by the Russian Ministry of Industry and Science as part of the Priority Objective on Developing New Biotechnology Research Areas and Ensuring Biosafety. Translated from the Russian by Kelly Robbins.

Title of Project	Financial Support (in rubles)
Development of methods for using heat shock protein to eliminate postoperative scarring	3.5 million
Study of processes involved in the synthesis of physiologically active proteins in cell-free systems	3 million
Creation of a transgenic potato resistant to viroidal, viral, and bacterial infections	2.5 million
Study of pharmacological properties of endogenous peptides (functional protein fragments)	4 million
Development of stem cell-based technologies for cell replacement therapy	3.4 million
Study of regulatory elements determining the boundaries of human genome domains and the effectiveness of their expression, as well as their use in improving genetic engineering methodologies	3.2 million
Development of nuclear magnetic resonance technologies and associated software for structural-functional proteomics and bioengineering	2.5 million
Development of microchip-based methods for analyzing biotoxins	2.2 million
Creation of a system for targeted delivery of gene therapy constructs based on hepatitis C (HCV) virions	4 million
Development of methods for three-dimensional spectral microtomography for studying cell transport and interactions of proteins and peptides	1.7 million
New methods of molecular modeling and molecular dynamics for structure-function analysis of proteins and peptides	3 million
Application of modern biotechnology approaches for increasing the effectiveness of anti-tumor gene therapy preparations	3 million
Study of the role of serine-threonine protein kinase of actinomycetes in regulating antibiotic resistance	3.3 million
Search for producers of biologically-active substances with hypolipidemic properties	2 million
Synthesis and determination of the structure and biological activity of new productive fluorquinolones	2.3 million
TOTAL	60 million[a]

[a]The exchange rate in 2003 was 30.7 rubles = $1.

Appendix M

Test Systems and Other Products Being Developed in Russian Laboratories[1]

The following new test systems have been proposed:

- Biosensor biochips for diagnosis of hepatitis B and C (by the Institute of Biomedical Chemistry);
- A test system for quantitative assessment of hepatitis B virus DNA using the competitive polymerase chain reaction (PCR) method;
- A test system for quantitative assessment of the content of hepatitis C virus RNA in blood serum using the reverse transcription polymerase chain reaction (RT PCR) method in conjunction with an internal standard (by the Scientific Center of Hematology);
- A diagnostic test usable not only for identification of hepatitis C virus, but also for the study of the seroconversion process during acute and chronic periods of the disease;
- Test systems for detection of antibodies of classes M and G to hepatitis C virus based on immunoenzyme analysis;
- A peptide-based diagnostic test usable for identification of hepatitis C virus (by the Ivanovsky Institute of Virology);
- A test system for determination of the reproduction level of Aleutian mink disease using the dot blot hybridization method;
- A PCR analysis-based test system for study of mixtures (pools) of blood to detect HIV genetic material (by the Andzhaparidze Institute for Viral Drug Research);

[1]Translated from the Russian by Supernova Translations.com.

- An immunoenzyme analysis-based test system for detection of HIV-1 sub-types, O type, and HIV-2, all of which are of special relevance for Russia;
- An immunoenzyme analysis-based test system for detection of the Crimean Fever virus antigen;
- An immunoenzyme analysis-based test system for detection of class G antibodies to the Congo-Crimean Hemorrhagic Fever virus;
- An immunoenzyme analysis-based test system for detection of arboviral infections, West Nile virus (by the Ivanovsky Institute of Virology);
- Diagnostic test systems for indication of antibodies to Respiratory Syncytial Virus (RSV), including immunoenzyme-based test systems, for identification of antibodies of different IgG subclasses (by the Institute for Influenza Research of the Northeastern Branch of the Russian Academy of Medical Sciences);
- A high-sensitivity express PCR method of tuberculosis mycobacteria detection (by the Central Institute for Tuberculosis Research);
- An immunoenzyme analysis-based test system for detection of anti-chlamydial antibodies in human blood sera using monoclonal genus-specific antichlamydial antibodies (by the Andzhaparidze Institute for Viral Drug Research);
- A test system for detection of Ureaplasma in biosamples through immunofluorescence reaction;
- A set of salmonellosis serological reagents B, C, D, and E for coagglutination reactions as a method of express diagnostics of intestinal infections;
- A test system for identification of cytokine-associated proteins from *Helicobacter pylori* in biological samples from infected persons through coagglutination reactions (by the Gamaleya Institute of Epidemiology and Microbiology);
- An immunoenzyme analysis-based test system for detection of antibodies to conditionally pathogenic bacteria (humoral immunity assessment);
- A selective growth medium for salmonellosis diagnostics (by the Mechnikov Institute for Vaccine and Serum Research);
- An immunoenzyme test system for laboratory-based diagnostics of early stages of Lyme borreliosis (by the Institute of Biochemistry of the Siberian Branch of the Russian Academy of Medical Sciences);
- Immunoenzyme reagents for detection of antibodies specific to testicular antigens that can be used for oncological diagnostics and assessment of effectiveness of tumor treatment (by the Institute of Clinical Immunology of the Siberian Branch of the Russian Academy of Medical Sciences);
- The STG-IFA immunoenzyme kit for detection of somatotropic hormone;
- The TTG-IFA immunoenzyme kit for detection of thyrotropic hormone;
- The AFP-IFA immunoenzyme kit for detection of alpha-fetoprotein;
- The HCG-IFA immunoenzyme kit for detection of human chorionic gonadotropin (by the Institute for Human Morphology Research);
- An immunoenzyme set for detection of prostatic specific antigen in blood serum (by the Russian Scientific Center of Oncology);

- An immunochemical test system for diagnostics of perinatal damage to the nervous system (by the Scientific Center of Mental Welfare);
- A set of chemicals for quantitative assessment based on immunoenzyme analysis of total IgE in blood serum for allergy diagnostics (by the Mechnikov Institute for Vaccine and Serum Research);
- An immunoenzyme system for testing the effectiveness of the monoclonal drug Anti-CD20 Mabter by detection of antibodies in peripheral blood and spinal fluid;
- A test system for determination of von Willebrant Factor level in blood plasma;
- The Genamplanstin test system for determination of prothrombin time (by the Scientific Center of Hematology);
- A study of the anti-aggregate effect of drugs by determining the degree of thrombocyte aggregation for diagnostics and treatment of diseases of the circulatory system (by the Institute of Narcology).

MEDICINAL PRODUCTS AND IMMUNOBIOLOGICAL DRUGS

Clinical trials of drugs developed at the Institute of Pharmacology of the Russian Academy of Medical Sciences, such as Afobazol, Selank (anxiolytics), Noopept (a neurotropic drug), and Tropoxin (an anti-migraine drug), have completely confirmed the experimentally established range of their pharmacological effectiveness (by the Institute of Pharmacology).

The neurotropic drug Semax was found to boost resistance to emotional stress, and this is of great importance from the standpoint of preventing stress conditions among persons whose professional activities involve elevated levels of risk (by the Anokhin Institute of Normal Physiology).

Industrial trial procedures have been drafted for production of the drug Agemfil.

The Russian Ministry of Health has developed and approved new regulatory and technical documentation including state standards governing the quality of such medicinal products as Adenin, plasma for fractioning, 5, 10, and 20 percent Albumin solution, Polyamine (by the Scientific Center of Hematology).

More than 770 new derivatives of glycopeptide antibiotics have been synthesized. A new class of synthetic equivalents of anthracycline antibiotics (the naphtoindolochtnons, which are active against anthracycline-resistant tumors) has been discovered (by the Institute for Research and Discovery of New Antibiotics).

A new drug, Affinoleikin, has been developed to treat psoriasis and atopic dermatitis.

A model has been designed for aluminum-hydroxide-adsorbed diphtheria anatoxin vaccine enriched with corynebacterial affinitins (derivatives of fibronectin and plasminogen) and possessing a higher specific immunogenicity compared to the commercially available drug (by the Mechnikov Institute for Vaccine and Serum Research).

A vaccine-usable strain (ERA-CB 20M) of fixed rabies has been obtained (by the Ivanovsky Institute of Virology in collaboration with the Narvak Stock Company).

The following vaccines have been created:

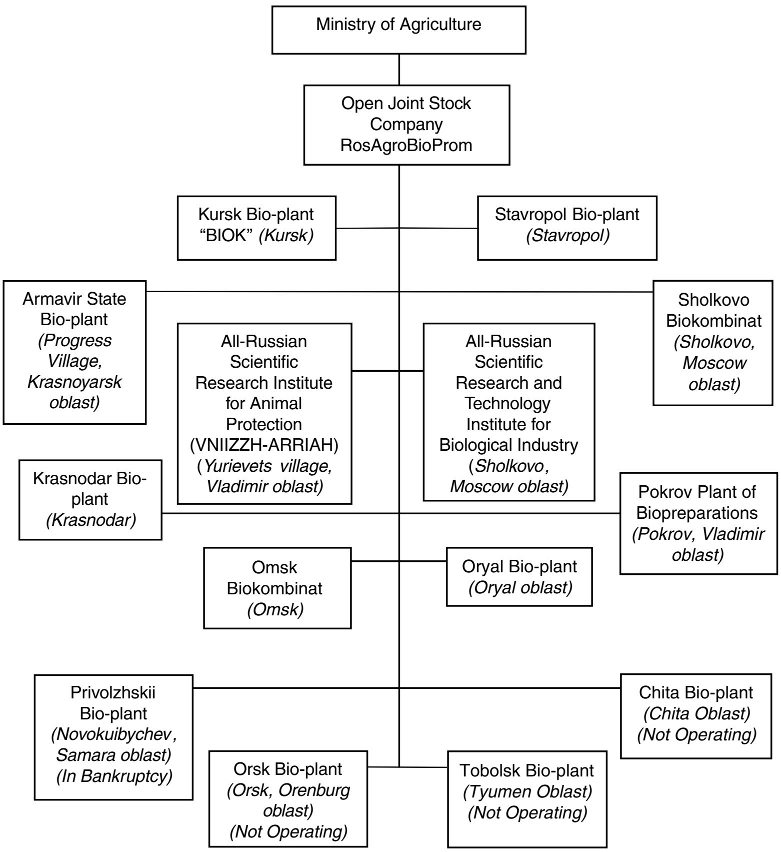
- HIV/AIDS vaccine based on the genetically-engineered drug Vichrepol (by the Ivanovsky Institute of Virology in collaboration with the Institute of Immunology of the Russian Ministry of Health)
- combined mumps-measles vaccine (by the Andzhaparidze Institute for Viral Drug Research)
- multi-component vaccine from conditionally pathogenic bacteria for prophylaxis of acute respiratory infections of non-influenza nature (by the Mechnikov Institute for Vaccine and Serum Research)

A highly-specific serum for diagnostics of staphylococcus has been obtained.

SOURCE: Ministry of Health (2003).

Appendix N

RosAgroBioProm Organizational Structure[1]



SOURCE: "Rosagrobioprom" report delivered by Monterey Institute of International Studies under Contract #NP-2003-18/BenOuagrham, task d) with CRDF/BII, January 8, 2004, 3.

[1] As of October 2004.

Appendix O

Activities of Russian Research Institutes in Developing Vaccines for Human Use

Vaccines Developed and Produced in Russia

- Measles/mumps
- Viral Hepatitis A
- Viral Hepatitis B
- Influenza

Vaccines under Development in Russia

- HIV
- Viral Hepatitis C
- SARS
- RSV
- Adenovirus
- Rubella
- Meningococal Meningitis
- Smallpox

SOURCE: Russian Academy of Medical Sciences, (2003).

Appendix P

Regulation of the Russian Government on Licensing Activities Connected with the Use of Infectious Disease Antidotes, No. 731[1]

Approved
by a resolution of the Government
of the Russian Federation
July 4, 2002, No. 501

STATUTE ON LICENSING OF ACTIVITIES ASSOCIATED WITH PATHOGENIC AGENTS OF INFECTIOUS DISEASES

(Resolution of the Russian Government, as revised October 3, 2002, No. 731)

1. This statute defines the protocol for the licensing of activities associated with pathogenic agents of infectious diseases by legal entities or individual entrepreneurs.

2. Activities associated with the use of agents of infectious diseases, including those common to humans and animals are subject to state licensing. These include microorganisms, including genetically modified ones, bacterial toxins, protozoans, helminths and biological poisons of pathogenicity groups I – IV, their industrial and archival strains, sanitary-indicative microorganisms, and materials contaminated or suspected to be contaminated with infectious disease agents of pathogenicity groups I – IV.

[1]Translated from the Russian by Supernova Translations.com.

3. Licensing of activities associated with pathogenic infectious disease agents is conducted by the Ministry of Health of the Russian Federation, hereinafter referred to as the "licensing authority."

4. Licensing requirements and conditions for engaging in activities associated with pathogenic infectious disease agents are as follows:

a. The license applicant or licensee must possess production facilities compliant with norms and rules established by the state and belonging to him on terms of ownership or any other legal terms (and in case of operations with infectious disease agents of pathogenicity groups I – II, the facilities must be equipped with protective devices and an alarm system), as well as equipment, instruments, and anything else necessary to conduct the activities subject to licensing;

b. Sanitary and epidemiological norms and rules established by the state for operations with infectious disease agents of pathogenicity groups I – IV must be observed;

c. Employees of legal entities and individual entrepreneurs alike must possess education or specialized vocational training in accordance with the requirements and nature of their jobs.

5. To obtain a license, applicants must submit the following documents to the licensing authority:

a. License request, which includes:

i. For a legal entity: name, form of organizational and legal ownership, and location, as well as locations of its territorially-autonomous subsidiaries and facilities to be used for activities subject to licensing;

ii. For an individual entrepreneur: last name, first name, patronymic, place of residence, personal identification information, and location of business;

iii. A description of activities subject to licensing that the legal entity or individual entrepreneur in question intends to conduct;

b. Copies of articles of association and of documents certifying that the legal entity is listed in the Unified Legal Entity Register.

(Resolution of the Russian Government, as revised October 3, 2002, No. 731)
(See previous version of the text)

i. A copy of the state registration certificate of the license applicant as an individual entrepreneur;

c. A copy of the license applicant's tax registration certificate;

d. Document confirming payment of fees for the licensing authority's review of the applicant's license request;

e. Copies of documents confirming the expertise of the individual entrepreneur and employees of the legal entity;

f. A copy of a legally-issued certificate confirming compliance with sanitary and epidemiological norms and rules.

6. Documents submitted in order to obtain a license are accepted with reference to an inventory list, a copy of which, with an indication of date of acceptance, is forwarded by the licensing authority to the applicant.

Copies of non-notarized documents are accepted upon presentation of the originals.

It is unacceptable to require the license applicant to submit documents not specified in this statute.

Submission of untrue, inaccurate, obsolete, or incomplete information by the license applicant is punishable under the laws of the Russian Federation.

7. Licenses for activities associated with use of infectious diseases agents are issued for a five-year term.

8. The licensing authority makes its determination on granting or refusing the license request within 60 days after the date when the request, along with all necessary documents, was received.

9. If the license is lost, the licensee has the right to obtain a duplicate thereof.

10. If the licensee has territorially autonomous subsidiaries and facilities to be used for activities subject to licensing, certified copies of the license corresponding to the number of such subsidiaries and facilities will be issued by the licensing authority in addition to the original license.

11. Within five days after its determination of approval, extension, re-licensing, suspension, or nullification of the license, the licensing authority must provide written notification to the licensee, the appropriate tax authorities, and the State Sanitary and Epidemiological Surveillance Center.

12. Within fifteen days after any change of domicile or location of territorially autonomous subsidiaries and facilities to be used for activities subject to licensing, the licensee must notify the licensing authority in writing.

13. The licensing authority maintains a register of licenses, in which the following is indicated:

a. Name of the licensing authority;

b. Activities subject to licensing;

c. Information regarding the licensee:

i. For a legal entity: name, form of organizational and legal ownership and location of the legal entity, as well as locations of its territorially autonomous subsidiaries and facilities to be used for activities subject to licensing;

ii. For an individual entrepreneur: last name, first name, patronymic, place of residence, personal identification information, as well as location of business for activities subject to licensing;

iii. Licensee code identifier (according to the Russian National Registry of Enterprises and Organizations) and taxpayer identification number;

iv. Date of license approval decision;

v. License number;

vi. Term of license validity;

vii. Information regarding registration of the license in the license register;

viii. Information regarding extension of the term of license validity;

ix. Information regarding re-licensing;

x. Grounds for and dates of suspension and renewal of the license;

xi. Grounds for and date of nullification the license.

14. Through scheduled and unscheduled inspections, the licensing authority oversees, within the bounds of its expertise, the licensee's compliance with license requirements and conditions.

Scheduled inspections are conducted no more than once every two years.

Unscheduled inspections are conducted to verify that the licensee has corrected violations discovered during a scheduled inspection, or in the event that the licensing authority should receive from a state authority, legal entity, or private individual any information (confirmed by documents and other proof) regarding violation by the licensee of license requirements and conditions.

The licensing authority shall notify the licensee of an upcoming inspection ten days prior to its commencement.

The licensee must provide conditions for the licensing authority to conduct its inspections, including by providing information and documentation.

The duration of an inspection must not exceed one month.

Inspections are conducted on the basis of the licensing authority's order, which specifies the licensee, time frame for inspection, and members of the inspection team. Inspection results are documented in an inspection report (in duplicate), which spells out specific violations and deadlines by which they must be corrected. One copy of the report is given to the licensee against his signature.

The licensee notifies the licensing authority in writing of correction of the violations by the deadline specified in the inspection report.

15. When conducting its licensing activity, the licensing authority operates in compliance with the Federal Law on Licensing of Selected Types of Activities.

SOURCE: Russian Federation (2002).

Appendix Q

Bioengagement Programs Financed by the United States Government

U.S. DEPARTMENT OF AGRICULTURE

Agricultral Research Service (ARS)-Former Soviet Union Scientific Cooperative Program (Funding for this program is received from the Department of State)

History

In 1998, the ARS initiated a program designed to provide opportunities for scientific cooperation between ARS scientists and scientists in research institutes of the Former Soviet Union (FSU) countries. The objectives are:

- to advance agricultural science by establishing new expertise in FSU countries
- to enhance the effectiveness and productivity of ARS research programs
- to improve the economy of FSU countries through advances in agricultural technology
- to reduce the threat of biological weapon (BW) development and usage in the world

Program Philosophy

- establish collaborative, mutually beneficial research projects
- develop proposals jointly (principal investigators from FSU and ARS)
- maintain substantial contact between ARS and FSU scientists

Program Model

The program endeavors to foster close cooperation between ARS and FSU scientists. Project ideas may come from either side, but the final project is developed jointly.

For further information, please see: http://iapreview.ars.usda.gov/research/programs/docs.htm?docid=987&page=2

U.S. DEPARTMENT OF DEFENSE

Cooperative Threat Reduction: Russia Programs

A. Biological Weapons Proliferation Prevention Security Enhancements

Locations

- Current: Obolensk (SRCAM), Novosibirsk (VECTOR), Golitsino, Pokrov

Project Description

- Enhance BioSecurity and BioSafety at Biological Research and Production Centers (BRPCs) to ensure secure and safe storage and handling of biological pathogens

For further information, please see: http://www.dtra.mil

B. Biological Weapons Proliferation Prevention Cooperative BioDefense Research

Locations

- Current: Obolensk (SRCAM), Novosibirsk (VECTOR), Moscow (RCMDT), Serpukhov (RCTHRB), St. Petersburg (SRIHPB)
- Potential: Sergiev Posad, Lyubuchany, Saratov, Volgograd, Rostov, Stravropol, Kirov, Yekaterinburg, Irkutsk, Kazan

Project Description

- Prevent proliferation of BW Biotechnology, increase transparency, and enhance U.S. force protection capabilities through research projects with former BW scientists at BRPCs

For further information, please see: http://www.dtra.mil

C. Biological Weapons Proliferation Prevention Dismantlement

Locations

- Current: Novosibirsk (VECTOR), Obolensk (SRCAM), Golitsino, Pokrov

Project Description

- Eliminate infrastructure and equipment at BRPCs that have BW capability and/or create barriers to involvement by Western commercial, non-governmental, or government entities

For further information, please see: http://www.dtra.mil

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of Global Health Affairs

A. HHS Biotechnology Engagement Program (BTEP)

Background

For nearly 30 years, Department of Health and Human Services (HHS) scientists have been involved in cooperative biomedical research with the former Soviet Union on polio, influenza, diphtheria, radiation health effects, and more recently, tuberculosis and other dangerous pathogens such as West Nile encephalitis. At the request of the Departments of State and Defense, HHS has developed a State-Department funded Biotechnology Engagement Program (BTEP) to "engage" former Soviet weapons scientists in collaborative research on applied high-priority public health problems.

The HHS BTEP supports broad U.S. policy goals of integrating Eurasian scientists into the international community; reducing the risk of proliferation of weapons of mass destruction expertise; increasing transparency at former Soviet biological weapons research sites; and redirecting bio technology expertise to peaceful research in areas of urgent public health needs.

Program Description

- The Office of Global Health Affairs has established a partner agreement with the International Science and Technology Center (ISTC) for funding and managing projects in Russia and the NIS.
- HHS experts have participated in workshops and site visits to develop a targeted set of projects focused around high priority public health needs in Russia and N. Eurasia and has worked with the Ministries of Health to help determine these priorities (TB, Hepatitis, HIV/AIDS, Variola, etc.).
- Scientists from the Centers for Disease Control and Prevention, National Institutes of Health, and Food and Drug Administration have worked with Rus-

sian and N. Eurasian colleagues to develop proposals under HHS and ISTC guidelines.

- Support will be provided for workshops and training on such topics as emerging and reemerging infectious diseases and grant proposal development to help mainstream otherwise isolated scientists.

For further information, please see: http://www.hhs.gov/ogha/europeaffairsdhhs.shtml

U.S. DEPARTMENT OF STATE

Office of Proliferation Threat Reduction

A. BioIndustry Initiative (BII)

BII was created to carry out two specific objectives:

I. Reconfiguration of former Biological Weapons Production Facilities

The Initiative seeks to engage and strategically transform former Soviet biological production facilities, technology and expertise for sustainable, commercial and peaceful applications.

II. Accelerate Drug and Vaccine Production

BII fosters partnerships between U.S. and Russian scientists for research and development to accelerate drug and vaccine production for highly infectious diseases that affect both the former Soviet Union and the world.

BII now receives annual funding from the U.S. Department of State's Office of Proliferation Threat Reduction, which supports both the Science Centers and the Bio/Chem-Redirect nonproliferation programs working in Eurasia.

Strategy

The Initiative selects projects based on merit. BII then invests significant effort into matching the best research or production institute with the appropriate industry partner to develop a strategic plan optimized for success. BII is able to support all aspects of a given project, from intellectual property management to product launch. While basic infrastructure upgrades and training to meet international requirements have become a hallmark of BII, all projects start with the appropriate due diligence. This strategy allows Russian entities working with BII viable commercial alternatives for research and production through constructive and cooperative mechanisms.

Partnership

Every effort begins with a partnership between BII and the Russian institution. Personal and institutional partnerships produce a beneficial amalgamation of ideas and practices to identify and develop innovative technology.

Versatility

BII has developed a variety of implementation networks, which provide a stream of expertise spanning the entire spectrum of functions, from preliminary scientific research and strategic business planning all the way to the final stages of a product launch.

Industry

Industry plays a central role in the BioIndustry Initiative. Western industry partners pursue fresh approaches to pipeline development or the optimization of production capacity.

Success

Diversification of funding and viability is the ultimate goal, whether that be the approval of an international research grant or the launch of a novel product.

For further information, please see: http://www.biistate.net

B. Science Centers Program

Background

Through the multilateral Science Centers in Moscow and Kyiv, the Department tries to guide collaborative research with former nuclear, missile, chemical, and biological institutes. Former weapons scientists in 10 former Soviet states are involved in U.S.-funded research in a wide variety of fields, including physics, environmental science, biology, informatics, chemistry, fission reaction, materials science, instrumentation, aerospace engineering, and others.

Funded projects involve collaboration with U.S. entities—DOE National Labs, academic institutions, private research entities, and foundations. If a U.S.-funded project results in intellectual property (IP), then the U.S. government (USG) has exclusive licensing rights to that IP in the United States.

The Science Centers Program also manages a Partner program through which other USG agencies or private entities, including commercial enterprises, may directly fund research while enjoying the management and diplomatic privileges of science center involvement.

C. U.S. Bio-Chem Redirect Program

Background

The Bio-Chem Redirect Program (BCR) is a targeted nonproliferation initiative funded by the Department of State's Nonproliferation, Antiterrorism, Demining and Related Initiatives account. BCR engages former Soviet biological and chemical weapons scientists in transparent and sustainable civilian research projects with U.S. collaborators.

The State Department provides funds to three U.S. agencies to implement the program: the U.S. Department of Health and Human Services, the U.S. Department of Agriculture, and the U.S. Environmental Protection Agency. These agencies work through the ISTC in Moscow and the Science and Technology Center in Ukraine, located in Kyiv, to implement the program. The program supports the following expenses: project salaries for Eurasian scientists possessing dual-use expertise; limited purchases of project-relevant laboratory equipment and reagents; and travel expenses for Eurasian scientists related to legitimate project needs, including scientific conferences, training, and meetings with their U.S. collaborators.

The program's primary nonproliferation mission is to redirect these Eurasian scientists to long-term sustainable activities in the civilian sphere. In addition, the program meets important U.S. research objectives in the following areas: global public health, livestock and plant health, environmental monitoring and remediation, and measures to combat biological and chemical terrorism.

Appendix R

International Programs and Projects of Special Significance to the Ministry of Health and Social Development[1]

- Program of Joint Activities to Overcome the Consequences of the Chernobyl Disaster under All-Union State Auspices for 2002-2005 (sponsor: Russian Ministry of Emergency Situations)
- Program of the World Health Organization (WHO) to Control Food-Borne Infections and Food Poisoning in Europe (sponsor: WHO)
- Influenza in Russia: the 2001-2002 Season (sponsor: WHO)
- World Health Study (sponsor: WHO)
- Epidemiological Study of the Causes of the Sharp Fall in Life Expectancy in Russia in the 1990s (sponsor: the European Union)
- International Association for the Promotion of Co-operation with Scientists from the Newly Independent States Program Indication on Novel Targets for Prevention of Apoptosis Induced by Prion Protein (sponsor: Fogarty International Center of the U.S. National Institutes of Health)
- Development of New Anti-Influenza Medications Based on Adamantane (sponsor: Fogarty International Center of the U.S. National Institutes of Health)
- Countrywide Integrated Noncommunicable Disease Intervention Program for Integrated Prophylaxis of Chronic Noninfectious Diseases (sponsor: National Public Health Institute, Helsinki, Finland)
- Cooperative Program of the U.S. Civilian Research and Development Foundation for the Former Soviet Union (sponsor: CRDF)

[1]Translated from the Russian by Kelly Robbins.

Four international projects:

- Ecology and Allergy
- Neurogene
- Nuclide-Pharm
- Projects in the Field of Informatics, Instrument Building, and Communications (sponsor of all four projects: Russian Ministry of Industry and Science)

Eight scientific projects (in the areas of oncology, vaccine development, and electromagnetic radiation) financed by the International Science and Technology Center

Three projects on problems of cardiology and ecology (HERO, MAGIC, and POLL-2002) financed by U.S. research centers

A TASIS-TEMPUS project on management training in the field of maternal and child health (sponsor: Cambridge University, England)

A project to create in the countries of the Commonwealth of Independent States a bank of thyroid tissue samples, nucleic acids, and other relevant data associated with the Chernobyl power plant accident (European Union)

SOURCE: Ministry of Health (2003).

Selected Bibliography

Bailus, A. N., Yu. T. Kalinin, A. V. Stepanov, and G. F. Astashkin. 2003. Gene-engineering insulin for humans: From idea to completion. In Biotechnology and Business. Proceedings of Third International Conference, sponsored by Biokhimmash, Moscow, April 21–22.

Ben Ouagrham, Sonia. 2004. Rosagrobioprom. Monterey, California.

Biokhimmash. 2003. Biotechnology and Business. Proceedings of Third International Conference, sponsored by Biokhimmash, Moscow, April 21–22.

BIOPREPARAT. 2003. Moscow.

Buga, P. G., E. N. Zamuruen, and Yu. A. Chernov. 1994. Higher Educational Institutions of Russia, Catalogue. Izhevsk: Udmurt University Press (in Russian).

CDC (Centers for Disease Control and Prevention). 1998a. Emerging Infectious Diseases: A Public Health Response. CDC, Atlanta.

———. 1998b. Preventing Emerging Infectious Diseases, A Strategy for the 21st Century. CDC, Atlanta (reprinted in 2000).

Dye, C. 2005. The Science of Social Diseases. Science 307: 181.

Gokhberg, L., and L. Mindeli. 1998. Research and Development in the Russian Higher Education Sector. Centre for Science Research and Statistics, Moscow.

International Science and Technology Center. 2004. Annual Report. Moscow.

Maksimova, L. 2003. Russian Pharmaceutical/Food Additives Market. U.S. Foreign Commercial Service, Moscow, December 23.

Medical Technology Holding. 2003. Advertising packet. June.

Ministry of Health. 2003. State Report about the Condition of Health of the Population of the Russian Federation in 2002. Moscow (in Russian).

———. 2004a. Concept of the Development of Public Health and Medical Science in the Russian Federation. (Approved by the Russian Government on November 5, 1997, No. 1837.) Moscow, January (in Russian).

———. 2004b. Information about the Structure of Expenditures of the Federal Budget for Financing Public Health (2001–2003). Moscow, January (in Russian).

———. 2004c. Progress in Implementing the Concept for Development of the Healthcare System and Medical Science: Tasks for the Periods 2001–2005 and 2006–2010. (Protocol no. 6.) Decision of the Collegium of the Ministry of Health, March 20–21, 2001. Moscow, January (in Russian).

Ministry of Industry, Science, and Technology and Russian Academy of Sciences. 2003. Russian Science and Technology at a Glance, 2002. Moscow.

———. 2005. Organizational Structure for Health Activities in Russia. Moscow.

National Science Foundation. 2004. Science and Engineering Indicators. Washington, D.C.

Natsionalnie Biotechnologii. 2004. Moscow (in Russian).

OECD (Organization for Economic Cooperation and Development). 2001. Bridging the Innovation Gap in Russia. Helsinki Seminar. Paris: OECD.

Onishchenko, G. G. 2002. Epidemiological Situation and Basic Directions of Activities for Its Stabilization. All-Russian Congress of Epidemiologists, Microbiologists, and Parasitologists, Moscow, March 26–28. Ministry of Health, Moscow (in Russian).

Onishchenko, G. G., L. S. Sandakhchiev, S. V. Netesov, and R. A. Martynuk. 2003. Bioterrorism: National and global threat. Vestnik of the Russian Academy of Sciences 73, no. 3 (March): 195 (in Russian).

Pokrovsky, V. I. 2002. Role of the science and practice of epidemiology for the health of the population. Epidemiology and Preventive Vaccinations (June): 2–7 (in Russian).

Raevsky, K. K. Military Medical Academy. 2002. Military Preventive Medicine: Problems and Perspectives. Proceedings of the First Congress on Military Medical Prevention Programs in the Armed Forces of the Russian Federation. St. Petersburg (in Russian).

Russian Academy of Medical Sciences. 2001. Moscow: RAMS Publishing House.

———. 2003. Moscow.

Russian Federation. 2002. Regulation on Licensing Activity Connected with the Use of Treatments of Infectious Diseases. (Approved by the Chairman of the Russian Government on July 4, No. 501). Moscow (in Russian).

Sandakhchiev, L. S. 2003. Presentation at Conference on Biosciences in Russia. Woods Hole, Mass., June.

Schweitzer, G. S. 2001. Industrial Perestroika: High Tech, Innovation, and Economic Growth in Russia. Arlington, Va.: Cameron Publication Services.

Stavropol Scientific Research Anti-plague Institute. 2003. Report on the Cooperative Work with WHO of the Scientific Research Center on Plague for 2003.

TEMPO Noncommercial Partnership Center of Modern Medical Technology. 2003. Biotechnology and Pharmaceutical Markets in Russia: Prospects for Development and Legal Base. Moscow.

USAID (U.S. Agency for International Development). 2003. USAID Fact Sheet. USAID, Moscow, June.

WHO (World Health Organization). 2003. WHO Country Cooperation Strategy, Russian Federation. Draft report, WHO, Moscow, September 1.

Zinov, V. G. 2003. Personnel situation in innovative businesses. In Biotechnology and Business. Proceedings of Third International Conference, sponsored by Biokhimmash, Moscow, April 21–22.

Zverev, V. 2003. Presentation at Conference on Biosciences in Russia. Woods Hole, Mass., July.