What's Over the Biotechnological Horizon?

R&D Trends in South African Civilian Biotechnology & Implications for Monitoring Future Dual Use Biotechnology Trends in the Developing World

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by

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EXECUTIVE SUMMARY

Summary and Conclusions

Over the past decade much of the nonproliferation efforts of the U.S. government aimed to prevent proliferation of technology and expertise from the former Soviet military-industrial complex. Potential biowarfare technology proliferation from developing countries received much less attention. This study addresses the gap by describing civilian biotechnology trends in South Africa that may be relevant for understanding dual use trends throughout the developing world.

South Africa is a useful case to examine because it has first-world science and industrial sectors capable of producing world-class chemical and biotechnology research and development. South Africa also has a history of covert weapons development. South Africa initiated a sophisticated secret biological and chemical program called Project Coast over two decades ago. While all of South Africa's weapons of mass destruction (WMD) programs were terminated before the political transition in 1994, several biowarfare proliferation concerns remain. These concerns are related to questions about where former scientists are today and how are they making a living. There are also concerns about what exactly was produced under the auspices of Project Coast and where undeclared biowarfare agents may exist today. The study does not focus on these proliferation threats but rather on new types of proliferation issues that are likely to emerge from the biological revolution currently underway throughout the world.[1] The current diffusion of biotechnology expertise, equipment and resources necessary to sophisticated biotechnology research and development throughout the developing world may create new dual use technologies and issues. The nature and extent of these problems are not yet understood. Emerging trends in the civilian research and development sectors of South Africa may provide some insights into wider global trends that may appear throughout the developing world as the current biological revolution progresses.

The three-part report surveys recent civilian biotechnology trends in South Africa in order to better understand future dual use proliferation concerns in South Africa and other developing countries.

Part I describes efforts by the South African government (SAG) to monitor civilian biotechnology research and developments at both public and private entities. Several difficulties and concerns arise as national regulators attempt to monitor potential dual use research and development activities in South Africa. Responsibility for monitoring potential misuse of biotechnology is spread across several government agencies. The supreme national regulatory agency in South Africa is the Non-Proliferation Committee (NPC). The NPC reports directly to the Cabinet and President on possible biological and chemical dual use sites. The NPC has the responsibility for implementing the Weapons of Mass Destruction Act of 1993 through on-site inspections of public and private research and development facilities that are capable of producing bio-chem agents. However, over the past decade the NPC has only conducted six formal on-site inspections. Only one of the inspections was at a government biological installation. The section also briefly describes other gaps and emerging problems in South Africa's counter-proliferation monitoring system that may pose additional problems in the future.

Part II surveys recent civilian biotechnology research and develop trends in the public and private sectors of South Africa. The survey is illustrative rather than comprehensive. At the time the research was conducted in 2003 there was no comprehensive list of biotechnology research institutes or biotechnology

[1] The research project agreement precluded me from talking with South Africans or Americans working for defense or intelligence agencies about dual use biotechnology issues. Thus, several proliferation questions are not addressed in the report. Instead, the report focuses on present and future trends in civilian biotechnology sectors, efforts of the South African government to monitor potential dual-use trends, and emerging concerns of regulators, researchers, and entrepreneurs involved in biotechnology research and development programs in the public and private sectors.

firms. Several different types of institutions that had the capacity to develop dual use biotechnologies were visited during a three-week research trip. The section also describes the National Biotechnology Initiative initiated in 2001 and the South African Bioinformatics Initiative (SANBI). The goal of SANBI is to link research units throughout the country, and eventually throughout Africa, into a computational network to help African researchers conduct state-of-the art bioinformatics research. The SANBI initiative is one of the most significant government sponsored programs underway in South Africa because it has the ambitious goal of linking centers of excellence throughout the African continent in a bioinformatics network that will allow researchers at many different locations to conduct sophisticated proteomics research projects. South African universities also offer graduate education programs in several different fields that employ sophisticated biotechnology techniques. Most graduate programs in science in South African universities today are actively recruiting students from African and Middle Eastern countries. At the same time that many students from Africa and the Middle East are encountering difficulties enrolling in graduate programs in Western countries, South African universities welcome foreign students into more affordable advance degree programs in microbiology, bioinformatics, and several other fields.

Another important initiative initiated by academicians in South Africa is the African Genomic Project. The program was initiated in 2002 with the goal of expanding the number of African researchers and biotechnology entrepreneurs who have access to the tools necessary to engage in sophisticated biological research and development. As the recent research and educational initiatives progress in future years, South Africa will become an increasingly important location for genomic and protenomics libraries, computer facilities, and graduate science programs for many scientists and aspiring scientists in Africa and the Middle East.

Part III summarizes the major findings and offers five policy recommendations for the United States Government (USG). Throughout the report attention is paid to policies, programs, research and development, and educational activities in South Africa that are useful for understanding future biotechnology trends throughout the developing world.

Today there are about 500 biotechnology projects spread over seven sectors in South Africa. At the time the study was conducted no one knew how many public or private entities were using sophisticated biotechnologies. The government was in the process of completing the first national audit of civilian uses of biotechnology. The main product of the audit will be a list of biotechnology corporations and research units engaged in biotechnology research. While the size of South Africa's civilian biotechnology is still very small, the pattern of commercializing basic research mirrors the relationships found among government, industry, and universities and industrial laboratories in the United States and other developed countries a decade ago.

The most sophisticated applications are currently in the pharmaceutical and medical sectors. They are also the areas that are able to attract large amounts of private funds from grants and foreign investors. Important geographical hubs of biotechnology commercial research and development are located in the Western and Eastern Cape provinces. A host of research and development activities center around efforts to develop commercial products from the unique genes in the flora and fauna found around the Cape of South Africa. The Western Cape is the region of the country that is experiencing the most rapid growth of new biotechnology companies. Demand for several different types of products based on the unique gene pool of the region is projected to expand very rapidly in the near-term future. Industrial and animal husbandry applications are found throughout the country but the largest concentration of biotechnology programs are located in the high veld area of Johannesburg-Pretoria in Guetang Province and in Kwazulu-Natal Province near Durban. The use of microbicides is a small but growing technology in mining and environmental sectors. For decades, older biotechnology techniques are also employed in the wine and beer industry.

Genetic modification (GM) research has also been practiced in South Africa agriculture for over twenty-five years. In fact, several South African agricultural researchers are entering their third decade of research after having lead global efforts to develop seeds and plants that are adapted to the local environment. Four GM crops have been approved for commercial release. In 2000, with almost 200,000 hectares planted with transgenic crops, South Africa ranked fifth in the world in area planted with transgenic crops.[2] While there is a small and growing GM protest movement in South Africa, most members of the research community and the South African government believe that GM agricultural products are a crucial part of future strategies for meeting future food needs throughout Africa.

A major change in biotechnology research and development during the last decade occurred as most of the larger foreign multinationals spun-off their biotechnology divisions or closed down unprofitable operations in South Africa. This trend is widely viewed by industry analysts and participants as a continuation of the more general disinvestments trend evident during the final decade of apartheid. High rates of crime were also cited by experts as an additional factor in the calculations of foreign corporations. During the 1990s several large South African firms also sold off their biotechnology research and development units because they were viewed as high-risk entities that would require years before a profitable product would reach the commercialization stage.

A couple of dozen biotechnology start-up companies were formed in recent years to fill the void left by big corporations or to commercialize research and development work originally conducted in universities or large corporate scientific divisions. Several small biotechnology companies were prompted to leave universities and develop biotech start-up firms during the past five years because of a recent tightening of intellectual property rules in universities. Most South African universities today, unlike the past, are attempting to share in the proceeds from biotechnology innovations. Thus, several new firms were formed during the past decade in order to exploit intellectual property and patents that were developed for the most part in university or industrial laboratories.

Nearly all of the newly formed biotechnology startup companies are attempting to develop unique niche applications in the agricultural, animal and human health, chemical, forestry, vaccine, mining, pharmaceutical, beer and wine industries. Biotechnology units across all of these sectors depend heavily on imported biotechnology applications, external funding, and international collaborations. However, there are also several dozen small South African privately owned biotechnology companies that have formed recently to commercialize unique intellectual properties and patents developed by South African researchers. Some of these commercial applications, especially in the area of vaccine development and drug delivery systems, use highly sophisticated, state-of-the art biotechnology processes and procedures.

The most important findings of the study are: 1) Current South African national counter-proliferation measures are inadequate for monitoring potential dual use civilian biotechnology research; 2) Several small biotechnology start-up companies in South Africa rent laboratory bench space to conduct pre-patent research at underutilized Technikons that were built during the apartheid era to educate non-white technicians; 3) At least half-a-dozen of these private firms are engaged in state-of-the-art biotechnology; 4) South Africa is a important location offering graduate training for biology and biotechnology for students from Africa and the Middle East; 5) the National Institute for Communicable Diseases (NICD) of South Africa played a vital role in monitoring the SARS epidemic in Africa last year for W.H.O. and has the human and biological resources to make a major contribution to the United States' global War on Terrorism; 6) Several research centers throughout Africa are conducting sophisticated biotechnology research and will soon gain access to a Cray super computer in South Africa that will facilitate even more sophisticated bioinformatics research.

[2] I would like to thank an anonymous reviewer for providing me with these two statistics.

The survey of civilian biotechnology trends in South Africa suggests extensive diffusion of sophisticated biotechnology research, development and knowledge capacities throughout the developing world. The implications from the extensive diffusion of biological knowledge and capacities necessary for conducting state-of-the art biotechnology research is not widely appreciated by members of the non-proliferation and counter-proliferation communities of the US government or the wider national-security community. However, this case study confirms that there has been a rapid spread of the knowledge necessary to conduct state-of-the art proteomics and genomic research that use sophisticated computational models to Africa. Several poor countries in Africa already have one or more modern facilities that have the capability to produce sophisticated biotechnology products. This situation underscores the fact that the USG now faces a fundamentally different set of proliferation problems and concerns in the effort to monitor potential dual use of civilian biotechnology than those associated with more familiar weapons of mass destruction proliferation threats. The survey of civilian biotechnology trends in South Africa and the realization that there are already several biotechnology islands of excellence throughout Africa also suggests that very different approaches may be necessary to understand, monitor, and manage potential dual uses of civilian biotechnology throughout the developing world than those currently being used.

Recommendations

The report offers five recommendations related to additional procedures that can be employed to monitor emerging trends in the "new biological world order." Each of these suggestions emphasizes a different approach than the reliance on technical means and spying that currently feeds many ongoing monitoring efforts or the emphasis on denial of access and control approaches underlying most non-proliferation measures. The recommended actions are intended to supplement rather than replace existing ways to monitoring potential proliferation threats stemming from civilian biotechnology research and development.

1) *The USG should make several modest strategic investments in promising private start-up biotech companies and establish new research partnerships between DOD researchers and researchers at a few universities involved in sophisticated biotechnology research in one or a few key countries in each sub-region of the developing world.*

In most cases, the lead country where cutting edge biotechnology is occurring will also be the regional hegemonic power. Thus, South Africa is the obvious candidate for investments and collaboration in Southern Africa. Egypt is a less obvious but important center of biotechnology education, research and development in North Africa. Nigeria has a biotechnology national plan but has not yet translated the plan into action. However, the large number of university and technological educational facilities, including several educational institutes in the northern, predominantly Muslim states, along with the ability of small biotech start-up companies to operate in this huge country undetected, suggest the need to monitor trends in this country as well. A similar set of countries can easily be identified for other regions or sub-regions of the world. For example, Brazil stands out as an obvious first candidate in Latin American. Brazil's national biotechnology plan has already served as a model for several developing countries, including state planners in South Africa involved in developing the National Biotechnology Initiative. Several cooperative arrangements between public and private entities already exit between Brazil and South Africa in the areas of pharmaceuticals and agriculture. Well-placed strategic investment in a few locations in key nation-states in several regions or sub-region of the developing world should provide added value in terms of obtaining additional information and insights about what is being developed by whom among groups of biotechnology researchers throughout the developing world.

2) *The USG should increase cooperation with the South African National Institute for Communicable Diseases (NICD)*is responsible for surveillance and management of infectious diseases throughout the African continent. The NICD is one of the only laboratories on the African continent that has a BL-4 laboratory. As one of the oldest research and public health laboratories on the continent, the NICD has an impressive network of professional contacts throughout the developing world. It's modest specimen culture library dates back to the 1970s. The infectious disease scientists are widely respected since none of the personnel worked on Project Coast projects. Moreover, the NICD routinely analyzes specimens from countries as far away as Pakistan.

3) *The USG should require an annual or biannual inter-agency status update report about key civilian biotechnology trends that may have dual use applications in the public and private sectors of the targeted nation-states and for each region in the developing world*.

The report should include inputs from the State Department Science and US Agency for International Development representatives working in the field in key countries in each region, along with inputs from Agriculture, Energy, and Environmental affairs, Dept. of Defense, Commerce, Dept. of Homeland Security, the CIA, FBI, and other executive agencies. Given their expanded role in health research, it would be also be useful to obtain input from government agencies involved in the health field (i.e. National Institute for Health, USAMRID), along with written inputs from non-governmental organizations.

4) *The USG should send one or more representatives to the 2004 African Genome Conference in Cairo*.

South Africa and Egypt are likely to remain the principle hubs of biotechnology activity on the continent in the future. However, coordination and cooperation among research institutions throughout Africa is increasing. Several research institutes in Kenya, Uganda, and Libya already have the capacity to engage in sophisticated dual use biotechnology research and development. The second African Genome conference will be held in Cairo during 2004. Participants are likely to include representatives from several well-respected agricultural research institutes in Kenya that are doing state-of-the art genetic modification research on maize, researchers from the Hilary Clinton Bioinformatics Center at Makerere University in Uganda, along with representatives from research institutes in Algeria, Morocco, and Libya will also attend. US representation at the second African Genome Conference would be an economical way to identify key individuals and biotechnology trends throughout the continent.

5) *The USG should provide assistance to the SAG to launch an initiative that* r*equires all public and private Biosafety laboratories in South Africa and throughout the continent that use South African bioinformatics computer or gene library resources to meet internationally accepted Good Laboratory Practices (GPL). Those that do not the meet should be the target of national or possibly even international inspection*.

The recommendation was made by Dr. Daan Goosen, a former Project Coast scientists, during an interview with the author in June, 2003. For Dr. Goosen, "open transparency and freedom of information are the key way to control biowarfare threats" at the scientific level. His recommendation for monitoring the civilian biotechnology sector is to "get more countries in the developing world on international laboratory standards" used by the United States, the EU, and the OECD. South Africa has a similar body that regulates Good Laboratory Practices (GLP) called the South African National Accreditation Service. This accreditation body certifies GLP based on an internationally recognized standard. The GLP systems of accreditation and regulation are based on "good faith" voluntary compliance so any lab that is not in compliance would be easier to spot once more countries adopted existing standards of accreditation and certification. While the approach does not address the problem of the "lab in the suburbs" or the bush, a focus on accrediting laboratories may be particularly well suited for developing countries such as South

Africa where the number of public projects and private start-up biotechnology companies are still relatively small and where everyone seems to know what other biotechnology researchers are doing.

All of the recommendations are intended to expand the information base about potential dual use activities and actors in developing countries. The recommendations are also designed to increase the number of collaborations activities between the USG and other public and private R&D groups in foreign countries in order to increase the talent and product pool available to the United States in ongoing effort to prevent, prepare for and manage the many crises that are likely to result from one ore more biowarfare attacks. The National Institute of Health has done an impressive job of identifying, investing, and collaborating with researchers working on promising lines of vaccine and drug development research in South Africa, I did not find any evidence of a parallel effort by DOD. In one instance, two DOD personnel visited a recently privatized South African firm, BioVac, after the 2001 terrorist attacks to inspect a large stock of smallpox vaccine. The Director of Research, Dr. Woolf Katz, had developed a large supply of smallpox vaccines while working at the State Vaccine Institute. Dr. Katz transferred the vaccine to BioVac and currently has enough smallpox vaccine at the plant outside Cape Town to vaccinate half of all Africans. The US government officials who visited BioVac judged the stored vaccine to be unusable for the US military because it was manufactured years ago using the dead virus method. However, the potential advantages of investing in BioVac for other reasons was apparently not considered at the time. BioVac, like most newly formed biotech startup companies in South Africa, are currently extremely interested in developing niche markets and products that will lead to future collaborations and investments by the USG or private US investors. However, nearly all of the South African biotechnology entrepreneurs interviewed reported that they were experiencing difficulties determining how to locate potentially relevant partners or clients within the U.S. government, particularly in the arena of national security. Nearly all of the new biotech companies are starved for capital and are looking towards for foreign investment sources and partners for their continued survival. In the case of BioVac, one of their most important collaborators and investors is a Cuban firm, Haber, with whom they are developing several different vaccines.

The second recommendation is also designed to expand the monitoring capabilities available to DOD and other relevant USG government analysts to obtain early warning regarding infectious diseases that may be intentional biowarfare attack. Additional links to the South African National Institute for Communicable Diseases would also expand the reach of DOD crisis management capabilities in the event of a massive biowarfare incidents. The USG National Institute of Health has developed an impressive network of researchers through a strategy of making strategic investments in collaborative research programs with several different groups of researchers in South Africa.

The third recommendation of a mandatory annual reporting was felt to be the most efficient and cost-effective way to get executive agencies within the U.S. government to communicate, compile, and circulate to relevant actors at all levels of government in the United States what is known about the civilian biotechnology activities of specific countries on a regular basis. There are obvious disconnects in the communication and information sharing procedures across agencies in Washington D.C. and even within the same embassy related to a host of new biosecurity issues. At least this was the impression I had after consulting with several dozen of USG employees in Washington D.C. and in South Africa who are experts in highly specialized functional areas. While an annual or biannual report is no panacea it would build in a requirement for periodic communication among and between different levels of the several USG agencies that are currently involved in monitoring emerging biowarfare threats abroad. Recommendation four and five represent additional relatively low cost approaches for managing new problems that may emerge from biotechnology commercial activities worldwide.

Section I

Monitoring Biowarfare Research and Development Trends in South Africa

1.0 Introduction: Why Study Biowarfare R&D Trends in South Africa

Over past decade much of the nonproliferation efforts of the U.S. government has focused on preventing proliferation of technology and expertise from the former Soviet military-industrial complex. Potential biowarfare technology proliferation from developing countries has received much less attention. This study seeks to fill the void by describing biotechnology trends in South Africa that may be relevant to the development of dual use capabilities throughout the developing world. South Africa is a useful first case to examine because it has first-world science and industrial sectors capable of producing world-class chemical and biotechnology R&D. South Africa also has a history of covert weapons development. South Africa initiated a sophisticated secret biological and chemical program called Project Coast nearly thirty years ago.

South Africa is also one of several major middle-level nation-state powers in the developing world that is pursuing civilian applications of state-of-the art biotechnology research in medicine, industrial production, environmental cleanup, and agriculture. The South African government launched a national biotechnology strategy modeled after Brazil's national biotechnology strategy in 2001. The goal is to expand the country's human and physical capacity to engage in third and forth generation civilian biotechnology research and development (R&D).[3]

South Africa also has a history of successfully competing in niche markets in several different sectors. Past successes are widely attributed to the fact that the country has a small but creative group of scientists and modern laboratory facilities. By understanding biotechnology R&D trends in South Africa, we may be in a better position to understand future likely trends, including possible dual use capabilities, throughout the developing world over the next couple of decades.

1.1a Purpose of the Study

The study surveys civilian biotechnology trends in South Africa in order to identify key emerging trends in potential dual-use civilian biotechnology sectors throughout the developing world. Section I focuses on government monitoring and regulatory activities and various sites that are of concern to governmental counter-proliferation monitors. Section II maps current civilian biotechnology research, development, and graduate education trends across several sectors of South African economy. The section identifies the main reasons why South Africa formulated a National Biotechnology, describes the program evolution and funding sources and the R&D activities of several innovative biotechnology startup companies. Some of their unique processes and products may also be of interest to US government agencies involved in the War on Terrorism. Throughout the study important trends that may be relevant to other developing countries, such as the widespread use of Technikons or trade schools by new biotech companies and the importance of hub countries for training future scientists in the region are identified. Part III summarizes findings related to the South African case and provides the rationale for four policy recommendations. Contact details for key individuals involved in genomic and proteomics research and

[3] For more details, see South Africa Government's A Biotechnology Strategy for South Africa, Ministry of Science and Technology, June 2001 (http://www.dst.gov.za/programmes/biodiversity/biotechstrategy.pdf).

development activities, including programs using state-of-the-art biotechnology processes and procedures, are found in Appendix A.

1.1b. Methodology: Section Criteria for Interviews & Entities

The criteria used to select individuals to interview at research institutions and private companies in South Africa and the United States was determined by the original research objectives of the proposal. The goal was to obtain data on several different types of research entities engaged in civilian biotechnology research and development with potential dual use applications.[4] The study selected R&D programs that had received funding from the South African government's two principle funds for stimulating biotechnology R&D: the Innovation Fund of the National Research Council and the ongoing grant proposal competition sponsored by the new Biological Research and Innovation Centers (BRICS). New private biotechnology start-up companies identified by business and intelligence analysts as being the most promising new, along with most of the firms that have received funding from a South Africa's new venture capital fund, BioVenture, were also visited. Several biotechnology R&D programs at four major research universities (University of Pretoria, University of KwaZulu, University of Cape Town, and Stellenbosch) were also visited. Other sites visited included two Agricultural Research Council institutes and the Center for Science and Industrial Research (CSIR). Many government officials involved in implementing the National Biotechnology Strategy were also interviewed in person and via email or phone. Because the scientific research community in South Africa is very small, it was possible to use a "snowball interviewing technique" that relied on the recommendations of interviewees to identify additional promising research activities during the interviews.

A few interviews were also conducted with former Project Coast scientists (i.e., Dr. Daan Goosen) and researchers who had worked with and knew many of the personnel well whom chosen to work for the former secret biowarfare program. Dr. Hack Jager, the former Director of Research and Development at Roodeplaat, the state veterinarian institute from which many veterinarians were recruited for Project Coast, Roodeplaat, was also interviewed for half-a day.

While interviews were not conducted with key individuals at all institutes and companies engaged in biotechnology research in South Africa, the study is a fairly comprehensive mapping of biotechnology R&D initiatives across several different research and development context and business sectors. This assessment is based on the fact that by the end of the third week of interviews in South Africa, most of the individuals mentioned as being key actors involved in biotechnology research and development across several sectors or related government programs had already been interviewed.[5]

1.2a Weapons of Mass Destruction Act and the Non-Proliferation Committee (NPC)

[4] It was not possible to use random sampling or conduct a survey because at the time of this research (Summer 2003) there was no universal list of public and private entities engaged in biotechnology R&D. A more systematic survey will be possible by next year because the EcoliBio Incubator at the Council on Science and Industrial Research (CSIR) in Pretoria, South Africa is currently completing a survey of all public and private entities involved in biotechnology research. For more details contact Paul Abrahams at CSIR (See Appendix A for contact information).

[5] The one key sector excluded from this study was defense. ASCO-DTRA requested that I not contact personnel working for the South African National Defense Force during the study. This exclusion is why there is no discussion of current R&D activities sponsored by the South African National Medical Service or interviews with the Defense Representative on the NPC in the report.

The statutory authority regulating dual-use biological agents in South Africa are amendments to the Weapons of Mass Destruction (WMD) Act of 1993. The act was passed after the de Klerk government dismantled a covert nuclear weapons program. Later amendments to the Act extended the jurisdiction to cover chemical and biological agents that can be used to make weapons. The amendments were also passed to ensure that South Africa honored her commitments to enforce the Biological Weapons Convention and the Chemical Weapons Convention.[6] Although South Africa only has observer status with the Australia Group, the national legislation incorporates the controlled substances on the Australia Group's D list and agents prohibited by the Chemical Weapons Convention.

A Council for the Non-Proliferation of Weapons of Mass Destruction, usually referred to as the Non-Proliferation Council (NPC), regulates the implementation of the WMD Act. The Non-Proliferation Council (NPC) is a cabinet level committee that reports directly to the President and acts as South Africa's control mechanism over all dual-use capabilities. The Chair of the NPC is Acting Director General of Foreign Affairs, Abdul Minty. Other members of the NPC represent relevant Cabinet Departments or serve as representatives of specific industrial sectors. These latter representatives are appointed by the Ministry of Trade and Industry to serve for a period of three-to-five years. The Vice Chair is currently empty. Two representatives are nominated by the Dept of Foreign Affairs, two by the Dept of Defense, one from Trade and Industry, one representative from the Atomic Energy Council, one from the Ministry of Minerals and Energy, and three appointees to represent the chemical, biological, and aeronautical industries. Dr. Southern, Director of the Biological Food Fine Chemicals and Fiber Association, is the current representative for the biotechnology industry.

South Africa today mirrors counter-proliferation structural problems facing the US government, albeit on a much smaller scale. The responsibility for managing dual use technology overlaps the jurisdiction of several different agencies. Overlapping and diverse jurisdiction means that several important areas of dual use technology are not covered by the NPC.[7] Nuclear materials and issues are handled by the Dept. of Minerals and Energy. The NPC also does not implement prohibitions of the Missile Control Regime, certain chemicals and agents (e.g., chemicals and microbes used to ferment wine), or agricultural products that have been genetically modified. Instead, the Department of Agriculture regulates agricultural research and trade. A much smaller regulatory agency, the Agricultural Research Medical Council, issues permits for animal vaccine research and regulates safe practices in animal research laboratories. The Dept. of Health regulates the movement of most human health products while the Medical Control Council (MCC) regulates the use of human subjects in clinical trials.

The South African government has made a conscious effort to ensure that the implementation of the WMD Act does not interfere with economic priorities. The wine and beer industry, ethanol fuels manufactured by SASOL, the oil from coal refinery, are all excluded from the jurisdiction of the NPC, as are other refineries and plastic polymers. There are also several exceptions in mining, including the exclusion of Ecoli used in mine clean ups. Who should regulate genetically modified agriculture is another area of increased concern to members of the NPC and an issue area that promises to become an increasingly contentious issue unless there is more agreement at the international level regarding the status of and how to regulate genetically modified agricultural products in international trade.

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[6] The specific amendments to the Non-Proliferation of Weapons of Mass Destruction Act, No. 87 of 1993 that deal with biological agents are amendments No. 50 of 1995 and No. 59 of 1996. The full text of the Act and subsequent amendments are available on-line at the South Africa government URLs listed at the end of the report.

[7] According to the amendments to the Act, the President and several members of the Cabinet acting on behalf of the President can declare anything a "controlled substance" that falls under the monitoring jurisdiction of the NPC.

The administrative agency for the NPC is the Dept. of Science and Technology (DST). DST is developing a computer-based system to track proscribed agents flowing into-and-out of South Africa.[8] The NPC is also in the process of identifying companies that transport biological pathogens on the controlled substance lists. The information will be added to an existing registry that contains information about what companies are working on and what facilities and equipment they have. The information being collected comes from voluntary self-reports by companies and universities and from past NPC inspections. The data entered into the NPC Registry include information about what companies are working on an inventory of facilities and equipment.[9] To date, Science and Industry personnel have visited the major research universities at Natal, Durban, Westville, Port Elizabeth, Rhodes, Stellenbosch, and Cape Town. However, no formal inspections of biological facilities have occurred yet (Interview with Ms. Melanie Reddiar, Assistant Director: Chemical and Biological Controls, Dept. of Trade and Industry, Pretoria, South Africa, June 25, 2003).

In working out inspection procedures, the WMD Committee uses an ad hoc protocol. The Committee is also sensitive to local legislation that specifies the requirements for prior notification before inspecting agents, technology or training programs. Much of the rest of the inspection protocol is a new field that was largely developed by academics as they went along. Most of those involved in past inspections felt that these visits to faculties were useful because they helped Committee members get a sense of what had been developed. NPC representatives reviewed list procedures that were required by laboratories with containment, interviewed key individuals, drew up an inspection schedule based on CWC. Additional protocols were in the process of being drafted at the time the negotiations for an Inspection Protocol were abandoned last year. (Interviews, Dr. Boettcher (June 25, 2003), Dr. Paterson (June 25, 2003); Ms. Reddiar (June 25, 2003), Dr. Southern (July 8, 2003).

The DST is also financing the nation-wide audit. The survey will provide a comprehensive list of all public and private entities in the country engaged in biotechnology R&D activities or who produce or work with biological agents. Personnel at the EcoliBio Incubator in Pretoria are conducting the national audit. The results should be completed and available to interested users before the end of 2003 (For contact details, See Dr. Abraham, Appendix A). Prior to the completion of the national audit there has not been a census or list of public and private entities engaged in biotechnology.

While the NPC has statutory power to make recommendations to the President, the activity of the NBC has been limited to date because of the small size of DST staff assigned to support the Committee. Only two bureaucrats in the DST are currently working full time to support the Committee by formulating proposed regulations, issue import and export permits, develop a computerized data base of all entities who work with biological or chemical agents on the control list, and support installation inspections.

A sense of urgency surrounding the development of protocols for biological and chemical facilities evidence during the Truth and Reconciliation Commission hearings has now dissipated. Reduced interest

[8] As noted above, biological imports related to human health are excluded since these fall under the responsibility of the responsibility of the Departments of Health. Agricultural products fall under the jurisdiction of the Department of Agriculture.

[9] To computerize data records, the NPC staff uses custom control eight digit codes. While the staff reports that they are not daunted by the size of the computer task facing them, they are finding that online application security is a major issue. Their model is similar to the one used in the United States. Openness and public access are important features of the system but confidentiality remains the highest priority (Interview with Mr. Arthur Boettcher, Deputy Director: Non-Proliferation & Space and Ms. Melanie Reddiar, Assistant Director: chemical and Biological Controls, Dept. of Trade and Industry, Pretoria, South Africa, June 25, 2003).

and concern on the part of the public may help explain why there have only been five NPC inspections during the life of the NPC. All but one of these has occurred at chemical producing facilities. There may be a lesson to derive from South Africa's experience for efforts to implement national on-site inspections of potential dual use facilities in other countries in the developing world. In South Africa these national inspections have proven to be extremely time consuming, costly, and limited exercises.

1.2b Potential dual use biotechnology sites

There are hundreds of government-affiliated research facilities where biological pathogens intended for weapons use could be produced. This section discusses a few locations that are mentioned frequently by South African and US government personnel as potential dual use sites. Table 1 lists several of these potential proliferation sites, the main reason for concern, the public or private status of the site, and points-of-contacts. The following discussion of potential government dual-use R&D facilities is illustrative rather than exhaustive.

Onderstepoort

Several former state parastatals institute remain subjects of concern for members of the NPC who focus on the possibility of dual use and potential abuse of facilities capable of producing sophisticated biological agents. One such institute is Onderstepoort, the only research institute subjected to a formal NPC biological on-site inspection. The inspection occurred in 2002. Officials from the NPC visited Onderstepoort, a public-private group of research institutes that manufactures animal vaccine, supports several animal and plant pathology laboratories, and supports various research programs under the auspices of the national Agriculture Research Council (ARC).

The Onderstepoort facilities, located just outside of Pretoria, house 16 different organizations including: the National Veterinary Faculty of the University of Pretoria, the Onderstepoort Biological Products Co., the Onderstepoort Veterinary Institute (OVI), and the Exotic Diseases Division (EDD). Many former government owned units, including OVI, are now partially privatized companies. For example, while biological production at OVI was privatized in 2000, the Dept of Public Work owns the buildings and the Dept of Agriculture, as the main regulator, receives copies of all official reports from the organization. Jurisdiction lines are further complicated by the fact that the physical facilities of several public-private and public organizations are mixed together on the same campus with only the Foot-and-Mouth Disease Vaccine Laboratory clearly separate in another facility near the OVI campus.

OVI is one of the oldest animal health research institute and pathology laboratories in the world. It was founded at the beginning of the 20th Century after South Africa experienced a devastated African Rinderpest epidemic from 1906-1907. After losing over five million cattle and an unknown amount of wildlife, the Transvaal Government established a Central Veterinary Laboratory to work on the prevention and cure, in addition to the diagnosis of animal diseases (Jager, 2000). OVI is also a world's leader in the production of animal vaccines, including the development of unique vaccines to prevent or control African horse sickness, bluetongue in sheep, botulism, anthrax, lumpy skin disease, ephemeral fever, anaplasmosis and heartwater. Researchers at OVI discovered that sweating sickness, caused by a toxin secreted by the bootlegged tick, could be treated with hyper immune serum. When Rift Valley fever became a widespread problem in South Africa, OVI developed the first animal vaccine using stem cells (Interview with Dr. Hans. G. Jager, former Director of Research and Development at Onderstepoort, July 1, 2003).

The OVI official web site notes that more attention has been placed recently "on the application of modern techniques for genetic manipulation towards the development of diagnostic probes and improved vaccines" in recent years (ARC-Onderstepoort Veterinary Institute, http://www.ovi.ac.za/).

Many veterinarians who worked at South Africa's former secret biological front company, Roodeplaat Research Laboratory (RRL) during the apartheid era, were recruited from Onderstepoort. Veterinarians served as senior managers and scientists in South Africa's past covert biological warfare programs because they were extremely well trained scientists having earned advanced degrees in two fields. Several of these scientists also had experience developing unique animal vaccines at Onderstepoort, and were motivated to engage in cutting edge research designed to develop to "reverse engineer" vaccines in order to develop biowarfare agents (Interview with Dr. Jager (July 1, 2003) and Dr. Daan Goosen, former employee at Onderstepoort and Project Coast Manager (June 26, 2003). While most Onderstepoort personnel were not involved in Project Coast activities, it remains one of the public-private institutions capable of producing large amounts of controlled biological agents. This is undoubtedly why Onderstepoort received the first NPC official inspection. No evidence of suspicious activities was found at OVI during NPC inspections. Although many Project Coast scientists returned to Onderstepoort after RRL closed, there has not been a systematic effort to monitoring the activities of these researchers. The South African government does not know where all of these former Project Coast employees work today.

Table 1
Potential Dual-use Sites, Concerns and POCs

Potential dual-use sites	**Potential Concerns**	**(Status of Research Institute) & Contact Information**
Onderstepoort (OVI)	-Largest public animal vaccine & research facility in SA 16 Divisions (BLS3 laboratories) -Manufacture capacity of bio-pathogens -Vaccine production using 1950's technology (African horse sickness, bluetongue virus, botulinum, anthrax, Rift Valley fever, brucellosis, Q fever, others) -Using GM techniques for R&D -Allegedly visits by Iranian and Iraqi scientists late 1990s -Many former Project Coast scientists employed again at OVI	(former parastatal, now a public-private partnership) ARC-Onderstepoort Veterinary Institute, Onderstepoort 0110, SA Tel: +27 (0) 12 529 9111 http://www.ovi.ac.za/ Relevant POCs: Prof Gerrit Viljoen, Biotech Division Dr. Anita Michel, Bacteriology Division Mrs. M. Scanlen, Biochemistry Manager
Biological Products Company	-Produces large amounts of biological agents, including most animal disease vaccines except for foot-and mouth	CEO: Dr Linda Makuleni, Vaccine Production Tel: +27 (0) 12 529 9111 http://www.ovi.ac.za/ (a public-private partnership since 2000)

Institute of Exotic Diseases (a former OVI unit once called the Foot & Mouth Institute)	-Animal disease vaccine production including Foot-and-Mouth Disease (FMD) (All FMD vaccine produced is sold solely to Dutch company, INTERVET, owned by Swedish Akzo Noble group. INTERVET sell vaccines to other parties) -2001 CRADA signed with Plum Island Disease Center, New York -PSL3 lab (Containment facility for working with highly contagious animal pathogens (i.e., Foot-and-Mouth disease (FMD) and African swine fever viruses) -Breeding Center for artificial insemination (AI) using cloning methods -R&D using RNA sequencing and large monoclonal antibiotic data bank -Diagnostic lab to include epidemiological data	(Public-private partnership) Dr. Wilna Voslo Tel: +27 (0) 12 529-9111 http://www.ovi.ac.za/main/divisions/edd.htm (Key POC: Dr. Gavin Thomson (For more details contact:Dr. Hans Jager, Avimune (EDMS) SPKhuck@avimune.co.za (former head of R&D at Onderstepoort)
BioCon	-Private lab for animal research opened up same time Project Coast RRL Lab closed (1990) -Several Project Coast scientist employed there -Allegations “broke,” “no contracts,” “no revenues” “out-of business in 2004” -Current status unknown (probably legally out-of-business but many interviewees referred to the “BioCon scientists”	(private company run by former Project Coast scientists; current status unknown) Dr. Brian Davies and Stiaan Wandrag, Director
Protechnik	-Contain six chemical labs test -R&D with toxic hazardous substances for SANDF labs -Manufactures gas masks & CBW protective clothing	Dr. P. Coleman Protechnik Laboratories (Pty) Ltd. Tel: +27 (0) 665 0231 e-mail: philipc@protechnik.co.za http://www.sadid.co.za/SADID_7/edition7/Pr

	-Provides technical assistance for CWC and BW Treaties -Recently hired microbiologist for advise DST on biological monitoring & inspections advise DST on biological monitoring & inspections	otech-nik/Protechnik.html (a former parastatal now a private company providing biological and chemical technical support to the SAG)

Biological Products Company

The Onderstepoort Veterinary Institute (OVI) built a modern vaccine factory in the 1960s. This facility continues to manufactured most state-produced animal vaccines today. In the early 1992, after the Agricultural Research Council (ARC) was formed, the vaccine factory was renamed the Onderstepoort Biological Products (OBP). OBP became a sub-directorate, and later a directorate of the National Dept. of Agriculture (NDA). The rationale for retaining the facility under the Agriculture Department rather than moving it to ARC was that it was a production rather than a research institute. Since 2000 a board of directors, appointed by the Minister of Agriculture has taken over most of the responsibilities of the NDA. The planning for this transformation, began in the late 1980s, was part of the larger government-wide effort to transform parastatals into private companies. Today, OBP is considered a private company with the State as the major shareholder (Jager, 2000). The laboratory space and equipment used by the biological agent unit at Onderstepoort was privatized as the Biological Products Company (OBP) in 2000.

While most Onderstepoort personnel were not involved in Project Coast activities, it remains one of the public-private institutions capable of producing large amounts of controlled biological agents. During the NPC official inspection at OVI no evidence of suspicious activities was found at any OVI research institute. For more details regarding the OBP products see Appendix B.

Exotic Diseases Division (EDD) or Exotic Diseases Institute

Another prominent research unit located at Onderstepoort is the Exotic Diseases Institute (also called the Exotic Diseaes Division of OVI). The unit is best known for work on highly contagious diseases of animals, particularly foot-and-mouth disease (FMD). According to the web site “it has established an international reputation as the most sophisticated FMD laboratory in Africa and one of the leading facilities in the world.” It houses a reference center for African swine fever and has attained pre-eminence in the study of the epizootiology of SAT-types of FMD virus, especially in relation to wildlife. The unit also has an extensive bank of virus strains was build up over the years, and the ability to characterize them by means of genetic RNA sequencing and monoclonal antibodies allow the selection of vaccine strains uniquely suited to niche markets”(Exotic Diseases Division, http://www.ovi.ac.za/main/divisions/edd.htm). The institute is located adjacent to but north of the campus at Onderstepoort. It was originally started as a breeding center where research on artificial insemination was conducted. In recent years the institute has conducted sophisticated research involving cloning and development of animal vaccines for various diseases.

Formerly called the Foot-and-Mouth Disease Institute, this ARC research institute was re-named the Institute of Exotic Diseases several years ago because the directors wanted to deal with more then FMD research and education. The former parastatal research institute that has been run as a public-private organization since the early 1990s. What this means in practice is that funding from the central government

has been greatly reduced and personnel are increasingly expected to bring in private funding in recent years. Similar to other public research units, the Institute of Exotic Diseases has also been under pressure since the early 1990s to become financially independent. The institute did not succeed in their initial goal of becoming financially self-sufficient hand during the 1990s and instead lost several research projects. Many skilled employees this and other ARC research institutes, after years of minimal annual pay increases, have emigrated or plan to emigrate. Today, while nominally a semi private entity is more government than private (email correspondence with Dr. Hans Jager, former Director of Research at Onderstepoort, October 21, 2003).

In an effort to generate revenue from private sources, the former Deputy Director of the Foot-and-Mouth Disease laboratory, Dr. Gavin Thomson, sold the rights for producing the FMD vaccine to the Dutch company, INTERVET (a subsidiary of the Swedish Akzo Noble group). This recent privitization initiative proved costly for the South African government in 2000 after a FMD outbreak occurred in South Africa. To manage the outbreak, the SAG was forced to purchase the locally produced FMD vaccine in US dollars from INTERVET.

In 2001 the Foot-and-Mouth Disease Institute signed a cooperative research arrangement with researchers at the Plum Island Animal Disease Center near Long Island, New York to develop vaccines for foot-and-mouth disease. A two-year Cooperative Research and Development Agreement (CRADA) financed the collaboration. Because the FMD virus changes constantly, scientists in the US and South Africa are using genetic engineering to develop better vaccines to keep up with the changes. According the EDD website, their lab was chosen "because of its international status and its work on a number of FMD strains indigenous to Africa…(for its) critical role in restricting the virus to the buffalo population in the Kruger National Park, thus maintaining the FMD freedom status of the country." Another reason for partnering with an international laboratory is that US companies cannot produce vaccines for FMD and the only place to even study FMD in the US is on Plum Island. Both countries will be able to use any vaccine that the scientists develop." Scientists on Plum Island have similar working arrangements with researchers from Brazil, China and Russia, but "the partnership with South Africa has advanced the farthest" (http://www.ovi.ac.za/main/divisions/edd.htm).

The history of research at this institute caused renewed concern among South African and US officials about the potential for dual use research at the Foot and Mouth Institute in 2001 (Interviews with US biowarfare experts, June 2003 and with Dr. Southern Interview, July 8, 2003). Following the anthrax attacks in the US in 2001 and a rash of anthrax hoaxes in South Africa in 2002, representatives of South Africa's NPC and the US Defense Department conducted several visits to the R&D facilities at the Foot and Mouth Unit. The South African government representatives were members of an Ad Hoc BWC Committee that included personnel from the South African National Medical Service, the South African National Defense Force, and Ministry of Foreign Affairs conducted a series of visits in 2002. Later in 2002 the South African government passed specific regulations related to biological agents. However, *the institute has not yet been subjected to an official inspection* (Interview, Dr. Southern, July 8, 2003). While no information is available regarding other research activities at the Institute, this site remains a focus of nonproliferation monitoring by the NPC. It is of special concern partly because so many experts believe that use of a naturally occurring pathogen, such as foot-and-mouth disease, is likely to be used by terrorists or political dissidents.

Status of Onderstepoort R&D today

Several interviewees claimed that Onderstepoort (OVI) is no longer capable of producing cutting-edge innovative animal research or vaccines because so many experienced researchers have left OVI over

the past decade. Dr. Jager cited the example of Gavin Thompson, the former head of Foot and Mouth research at OVI and a former Director at Onderstepoort, who is leaving for Kenya because he sees no future for himself at an institution where 80 per cent of the personnel must be non-white by 2004.[10] Several former OVI employees also expressed concerns about whether OVI is adhering to standard practices in producing and storing vaccines. During the apartheid era all vaccine stocks were destroyed as soon as they expired and Onderstepoort was well funded. The institution was an important one to the apartheid government because farmers were an important voting block for the former ruling party, the National Party (NP). Farmers counted on OVI to produce vaccines in emergencies and white farmers in turn, remained a loyal voting bloc for the NP. Dr. Jager noted that the world-class status of OVI's vaccine production started to deteriorate in the late 1980s. By 1987 or 1988 some products were being registered at OVI without a complete dossier.

Dr. Jaeger, who left OVI several years ago, no longer knows if vaccine stocks are still being destroyed on time. Oversight is now in the hands of a Board of Directors who are suppose to ensure that expired stocks are destroyed (Interview, July 1, 2003). Although the biological production facility was privatized in 2000, the national Dept. of Agriculture still receives all the reports generated by OVI personnel since the Agriculture Dept. is responsible for regulating OVI. The national Dept of Public Works owns all of the OVI buildings. Dr. Jager noted that when he was brought back to Onderstepoort after September 11, 2001 as a consultant, OVI was no longer producing vaccines "on standard." The possibility that OVI was no longer producing vaccines according to established laboratory practices disturbed Dr. Jaeger because Onderstepoort had a longstanding reputation as a premier animal research institution that produced quality animal vaccines and medicines.

Another former Onderstepoort and Project Coast scientist, Dr. D. Goosen, was even more disparaging about the quality of agents being produced at Onderstepoort today. Dr. Goosen alleged that virtually all ARC research had collapsed at Onderstepoort. Goosen claims that the Onderstepoort was now using 1950 technology to produce animal vaccines and that current managers had brought Iranian and Iraqi scientists to the facilities during the late 1990s (Interview with Dr. Daan Goosen, June 26, 2003). Other former employees who wished to remain anonymous made similar allegations.[11]

None of these allegations could be confirmed from independent sources. However, several academic researchers at University of Pretoria, who have longstanding research associations with Onderstepoort, and researchers at other research universities, painted a more mixed picture about the quality of research being conducted at different OVI research institutes. For example, Profs. M. and M. Wingfield and Prof. Dave Berger of FABI, University of Pretoria, claimed that at least a few of the

[10] Dr. du Plessis, Director of Infruitex, another ARC research institute, reported similar loss of staff due to a policy currently in place at his institute that calls for 80% of management personnel to be from staffed by previously disadvantaged groups within five years.

[11] Dr. Southern's impressions from his participation at the on-site visit confirmed the impression that the priority at Onderstepoort today is manufacturing rather than cutting-edge research. He noted that all facilities were open to inspectors. No one on the visit had the impression that certain back-room activities were being hidden. However, Dr. Southern's other comments might also be instructive for future efforts to inspect civilian faculties. He found that the production and research records were not kept in a consecutive fashion but rather kept on the basis of specific animal vaccine campaigns. This meant that there were not consecutive records kept and not detailed records of batch numbers. Language was also a problem since the records and employees at Onderstepoort worked in Afrikaans while the primary language of most inspectors was English.

remaining researchers at Onderstepoort are doing sophisticated and highly reputable biotechnology research that involves “third generation” biotechnology (Dr. B. and M Wingfield and Dr. Dave Berger interviews, June 26, 2003).

Research is playing a less prominent role in the activities of Onderstepoort today. At least that is the impression one gets from the statement by Dr Steve Cornelius, the new Director since 2001 in his public statement posted on the official web site. Dr. Cornelius emphasized that, “the ARC-OVI should go back to the farmers’ needs. This institute was founded because of livestock problems. It is known as an internationally recognized institute with the capacity and expertise to handle all animal diseases" (http://www.ovi.ac.za/).

Biocon

The Biocon Research Laboratory opened up simultaneously with the closure of Roodeplaat Research Labs (RRL), in 1990. RRL was one of the two major front companies for the South African Defence Force's former Biological and Chemical Warfare program, Project Coast. RRL was established in 1986 and closed in 1990 after pubic disclosures that it had been a front company for the apartheid government’s secret weapons program. Biocon, opened up as a private laboratory only a few kilometers away from where RRL had been located. Most interviewees were unclear about BioCon’s current status. Everyone agreed that the company had experienced financial troubles. Some interviewees thought the company was officially liquidated in 2000. However, several interviewees talked about the “BioCon scientists” as a group that was still in existence. The ambiguous current status of the company may be why many South Africans continue to believe that Biocon may still be involved in covert biowarfare activities. This suspicion is fueled by information being posted on the web by public interest groups that follow the activities of former Project Coast scientists.

For example, the public interest organization, South Africans for the Abolition of Vivisection (SAAV, http://www.saav.org.za/home.php), which is dedicated to the human treatment of animal, alleges that three Biocon’s directors were affiliated with Project Coast. The director of BioCon, Dr. Brian Davies, remains a controversial figure and the subject of investigations into his past activities. Biocon remains a “site of concern” for the NPC, other members of the South African government, and members of the informed public.

Concern about who former Project Coast scientists will work for in order to make a living increased in 2003. A rumor circulating recently that Biocon is bankrupt. Also in 2003 Dr. Goosen, a former Project Coast manager, sought money, relocation, and employment in the U.S for several former Project Coast scientists who were affiliated with Goosen’s biotech startup company. Several of the scientists who are working with Goosen were or still are employed by OBP, BioCon, and other struggling biotechnology companies. In an effort to negotiate relocation and jobs in the United States, Dr. Goosen disclosed that several of the Project Coast scientists who are capable of producing genetically enhanced biowarfare agents retain documents and pathogens that were suppose to have been destroyed when Project Coast was closed down (Warrwick, 2003). These continuing concerns underscore the long-term problems associated with how former biowarfare scientists make a living after the covert weapons program is dismantled. In the case of Project Coast, many former biowarfare scientists continue to experience difficulties finding well-paid employment. Several of the most prominent Project Coast scientists have either left the country or given up

research activities.[12] Others, such have Dr. Goosen have not and remain a subject of concern for South Africa and other several other governments.

Protechnik

Some of the difficulties involved in making distinctions between biological and chemical sites suspected of dual-use R&D is illustrated by Protechnik. Protechnik is a former parastatal that was involved in past covert weapons R&D. Protechnik was privatized in the early 1990s. Today, Protechnik is a public-private entity. The primary source of revenue for the company is the South African National Defense Force. Protechnik is South Africa's only designated Single, Small, and Scale Facility, which means it is the one location that can perform work on chemical warfare agents.

According to its web site (Protechnik Laboratories (Pty) Ltd. (http://www.sadid.co.za/SADID_7/edition7/Protechnik/Protechnik.html), "Protechnik specializes in testing, evaluating and providing technical support to South African National Defence Force (SANDF) personnel operating in hazardous and toxic environments." As an applied chemical laboratory "it which performs chemical Defence R&D project work and test and evaluation work for the Department of Defence" using six labs specializing in: chemistry, carbon, filtration, material evaluation, analysis and chromatography, and detection of chemical agents and their precursors. Protechnik also plays a role in advising both the Departments of Trade & Industry and Foreign Affairs on technical aspects related to the implementation of the Chemical Weapons Convention.

In addition to its involvement in CW non-proliferation, Protechnik is involved in government biological research activities designed to support government activities related to biowarfare as well as chemical agents. Protechnik remains a suspected site of covert research in part because of its involvement in secret weapons of mass destruction R&D during the apartheid era. At a minimum, scientists at Protechnik are probably following the research literature relevant to both chemical and biological warfare. Dr. Adi Peterson, Chief Operating Officer at the DST, acknowledged this possibility during our interview. Dr. Peterson also observed that "many specialists, including the scientists at Protechnik, are not that thrilled with the current Biotechnology Initiative" sponsored by his organization (DST, Pretoria, June 25, 2003). Moreover, since no one on the NPC or its staff is a microbiologist, a microbiologist was recently employed by Protechnik to provide technical support for the Non-Proliferation Council. Protechnik hired the microbiologist because one of its activities is to provide technical support for the biological work of the Non-Proliferation Council.

1.3 Human Health Regulation and Research

Some of the most sophisticated applications of biotechnology research are found in ongoing research in human health. Because of South Africa's biowarfare history, regulations and oversight of research involving human subjects are much more regulated today than a decade ago in South Africa. Table 2 summarizes three of the most important government bodies involved in regulation of research involving

[12] This emigration of Project Coast scientists caused problems for the prosecution at Dr. Woulter Basson's trial. Two key witnesses had emigrated to Canada and the prosecution was unable to call these two and several other Project Coast scientists because they were out of the country and the judge would not authorize payment to cover their travel funds. See Burger and Gould (2002). See also R. Block's (2002) article for a vignette of one senior Project Coast scientist's life since Project Coast was dismantled.

human health and health surveillance. The mission of each of these bodies and issues related to human health are summarized in Table 2 and described in detail in this section.

Table 2

Regulating and Monitoring Human Health Research

Agency	Mission	Contact Details
Medical Control Council (MCC)	-Regulates manufacturing, distribution, & sales of drugs -Registers generic formulations for infectious disease drugs in SA -Licenses medical products, practices, & sets standards for human health clinical trial (similar to FDA) -Supervises Clinical Trials Subcommittee with Nat'l Ethical Committees, university ethics committees, & SA Medical Association	Dr. Tony Mbewe, MCC Board Member http://www.mccza.com) See also Prof. Frank Otto Muller QdotPharma, George Tel: +27 448 441 560 Cell: 083 255 1227 Email: otto.muller@qdotpharma.com (One of the most knowledgeable scientists involved in human clinical trials since the 1970s)
Medical Research Council (MRC)	-To improve human health (similar mission to CDC) -Funds Pharmaceutical Technology Transfers of generic drugs used in SA -Funds R&D new drugs & vaccines	Dr. Tony Mbewe , Director of Research Medical Research Council Tygerberg, South Africa Tel: 27 21 938 0319 http://www.mrc.ac.za
National Institute for Communicable Diseases (NICD)	-Infectious disease surveillance (throughout Africa) -Diagnoses infectious disease specimens (BSL4) -R&D and Capacity building fo disease crises management capabilities throughout Africa	Dr. Barry Schoub, Executive Director, National Institute for Communicable Diseases (NICD) Johannesburg, SA Tel: +27113214201 schoub@niv.ac.za http://www.NIV.ac.za

1.3a Regulation of Human Health Research

The legacy of the past

Until the 1990s, Africa was a wide-open continent where western drugs could be marketed without the strict regulations of the west and where a large pool of human subjects could be recruited with few of the regulatory or ethical concerns than in place in western societies.[13] In South Africa it was possible to engage in certain medical research activities that were prohibited in the US, Europe and developed countries of Asia until a decade ago. Several incidents involving the illegal use of human subjects occurred during apartheid that involved members of the former South African Defense Force (SADF) or their dependents.

Testimony at the Truth and Reconciliation Commission hearings and at Dr. Woulter Basson's trial indicated that several SADF personnel were used as uninformed subjects in Project Coast experiments. Public disclosures and statements such as the above fueled widespread suspicions that some of the abuses from the past have not yet been disclosed. Until recently there were concerns that researchers involved in past secret biowarfare research might still be working in government service in regulatory positions. Organizational changes implemented during the 1990s, particular changes since the 1994 transition election, has led to most senior positions in regulatory agencies being held by personnel whose political loyalties reside with the ANC. Tightened regulatory oversight also makes it highly unlikely that South Africa is currently viewed an attractive site of illegal drug manufacturing or for illegal human trials by South African or foreign researchers. The norms and societal taboos against the illegal or immoral use of people as victims or subjects in human experiments that occurred under the auspices of Project Coast are so strong today that is unlikely to such activities run as legitimate medical research projects would be tolerated in either the military or civilian sectors.[14] However, the strength of prevailing professional norms could also serve as a powerful incentive to ensure that any covert biowarfare research and development activities was organized in such a way that peers in the scientific community would not know about the activities.

The Medical Control Council

The key actor in charge of ensuring that societal norms against illegal use of human subjects in medical experiments are upheld and that medical regulations are enforced is the Medical Control Council (MCC). The MCC's enforcement procedures and regulations have been strengthened and improved over the past 5-to-10 years. Currently, South Africa follows internationally recognized procedures and standards. A network of institutional research boards at universities and research institutes work closely with each other, the MCC, and the Medical Research Council (see below) to ensure that prevailing standards and ethical treatment of human subjects are enforced. A National Ethnic Committee formed by the Ministry of Health also serves as an overseer or ombudsman for researchers in universities who submit proposals for research to university committees. The South African Medical Association has a set of standards. An Ethics

[13] Dr. Katz, Director of the BioVac and the former State Vaccine Board, who worked as a consultant for the Medical Control Council confirmed that little control regulatory system in place until late 1970s (Interview, July 8, 2003).

[14] This view was expressed by Prof. Otto Muller, Managing Director, Director of Scientific & Regulatory Affairs, QdotPharma. Dr. Muller is one of the foremost researchers in South Africa involved in drug testing using human subjects (Interview July 3, 2003). Dr. Tony Mbewe, Director of Research, Medical Research Council and Board member, Medical Control Council expressed similar views in a phone interview (July 31, 2003).

Control Council is being established based on inputs from committees from all the major research institutes in order to establish a single system of accreditation, minimal requirements for training; and standard good clinical and research practices at all institutions that involve the use of human subjects. Thus, the current status quo is very different than during the apartheid era when enforcement of drug laws and clinical standards for human trials were more lax (see MCC web site for more details, http://www.mccza.com).

As the principle organization responsible for regulating and licensing medical products and clinical trials, the Medical Control Council (MCC) also has jurisdiction over the manufacture, distribution, sale, and marketing of medicines. The MCC regulates and licenses all medicines and complementary biological medicines, including some cosmetics and many veterinary medicines. Its regulatory functions and powers are similar to those of the Food and Drug Administration (FDA) in the United States.

The Clinical Trials Committee of the MCC regulates clinical trials of new drugs and vaccines. According to Dr. Tony Mbewe, Vice Chair Clinical Trails Committee of MCC, there has been an exponential increase in drug trials in South Africa, especially since 1994 (Phone interview with Dr. Tony Mbewe, July 31, 2003). Today there are over 400 new clinical trials annually in South Africa. Dr. Otto Muller, Managing Director of QdotPharma, the largest South African private medical research company in the country, explained that much of the increase is due to the increased number of foreign researchers and companies who now use South Africa for their clinical trails While many of the medical trials are Phase 1-3, a lot of multinational companies are also using South Africa today for their final, Phase IV trials.

Initiative for Pharmaceutical Technology Transfers (IPTT)

Another important medical R&D trend in South Africa today are government initiatives designed to lower the cost of drugs, especially medicines for infectious diseases such as HIV-AIDS. These initiatives are all designed to help build indigenous drug and vaccine capabilities. South African policies in the area of generic drugs is part of a larger struggle between developing countries and multinational drug companies over the issue of whether developing countries can lower the cost generic drugs to fight infectious disease epidemics in their country by producing drugs at home.

To begin the process of developing domestic drug production capacities, the South Africa government supported an Initiative for Pharmaceutical Technology Transfers (IPTT). IPTT is a non-profit company whose purpose is to facilitate the transfer of drug technologies from multinational pharmaceutical companies to developing counties. The formation of IPTT was supported initially by South Africa and Ethiopia and will soon include Algeria and Nigeria. The initiative represents another attempt of increasing the use of biotechnology R&D to expand the drug manufacturing capacity in South Africa and other African countries. To date, both Bristol-Kline and Scripps have been actively involved in the initiative. Another licensing agreement was recently completed between Kline-Smith and Aspen Pharmaceuticals, a South African based drug company. Thirteen antiviral drugs have been approved in recent years for use in South Africa. Most of the agreements are for some of the more commonly used antiviral drugs used by people with HIV.

The Medical Research Council

Another government organization that plays a key role in promoting human health is the Medical Research Council (MRC). The MRC serves a role analogous to the role of the National Institute of Health (NIH) in the United States. The mission of the MRC, established in 1969, is to “improve the nation's health status and quality of life” (http://www.mrc.ac.za).

The Minister of Health or the President appoints members of the Board of Director. An earlier forerunner of the modern MRC, established after World War II, promoted applied research in the area of human health. It was formed to fill a void since the science councils that were tasked with translating basic science research into practical applications, i.e., the Council for Science and Industrial Relations (CSIR), by mandate cannot work with human subjects. The official history of the MRC also credits the successful heart transplant conducted by Dr. Chris Barnard and his medical team in 1969 as another impetus for the establishment of an organization designed to promote medical research that could improve the lives of South Africans (Johnson-Barker, n.d., http://www.mrc.ac.za MRC web site)

The Medical Research Council (MRC) is a statutory body established under the Medicines and Related Substances Control Act, (Act 101 of 1965). The Minister of Health appoints most members. The President is also an official member of the Medical Control Council (MCC). MCC operates through external experts who are members of Council Committee structures. These experts evaluate data submitted by the pharmaceutical industry for purposes of registration and make recommendations regarding clinical trials for drugs. Experts on various committees also approve clinical drug and vaccine trials, except for most animal vaccines. These evaluators are from various academic institutions, mainly medical and pharmacy schools (http://www.mccza.com).[15]

In the early 1990s as apartheid crumbled, the MRC started to undergo major changes that led to increased communication and collaborations with outside researchers, a broadened scope of research interests to include the health of non-white South Africans, and a change in the ethnic background of the leadership and personnel of the organization. Over 20% of the personnel left in the early 1990s. After 1994, 14 (out of 17) new members of the Board of Directors were appointed. By the late 1990s the goal of having 75% of the MRC personnel be black South Africans was announced (http://www.mccza.com). These policy and personnel changes have had a large impact on the type of research funded by the agency. The personnel changes, that mirror what has occurred in nearly all national bureaucratic agencies since 1994, constitutes another important reason why it is highly unlikely that research sponsored by MRC, would include a covert or dual use component.

Today the MRC employs 200 people and has a budget of US$10 million. This budget is a sizable research one by South African standards and makes the MRC an influential player in medical research initiatives.[16] The MRC is a national organization with offices in Cape Town, Pretoria and Durban and a rural center at Hlabisa in KwaZulu-Natal. According to the web site, it currently supports a core of 250 scientists plus 100 technologists operating through 22 units (based at universities, including a quarter at historically disadvantaged institutions), research centers and 15 research programs. Internationally recognized scientists lead research programs. A total of 500 research projects have been undertaken recently and approximately 100 new projects are submitted every year. Additionally, the MRC supports another 300 scientists engaged in 300 three-year short-term research projects (self-initiated research).

[15] The Council has 11 technical committees, with 146 members from various institutions in the country. These include the Clinical Committee, Pharmaceutical and Analytical Committee, Clinical Trials Committee, Scheduling Committee, Veterinary Committee, Pharmacology Committee, Biological Committee, Complementary Medicines Committee, and African Traditional Medicines Committee.

[16] To understand why MRC is a major actor one must understand that science research in South Africa has been badly under funded for many years. According to the MRC web site "only six per cent of the science vote is allocated to the MRC. This is equivalent to 3% of the total health cost in the public sector, and contrasts sadly with the World Health Organization and World Bank recommended level of 2% in health research.

The MRC plays a key role in promoting biotechnology through the types of research project it funds. Much of the money to date has gone to support innovative lines of basic and applied research designed to develop vaccines to help combat infectious diseases common in South Africa. Top research priorities today include HIV/AIDS, tuberculosis, malaria, biotechnology, and human genomic. The MRC also provides research grants to support other public laboratories in South Africa, such as the National Health Laboratory Service, which has a Biosafety level 3 laboratory and the National Institute for Communicable Diseases, which has a Biosafety level 4 laboratory.[17] The MRC also supports researchers working in South African universities laboratories. The major research universities in South Africa all have several Biosafety level 3 laboratories.

MRC's funded projects are designed primarily to find new vaccines or drugs to manage HIV/AIDS, Tuberculosis, and other infectious disease. Foreign donors also provide financial support for nearly all MRC-sponsored projects. The most successful projects to date have been international collaborative efforts that have used state-of-the art biotechnology.

1.3b National Institute for Communicable Diseases (NICD)

Another public entity that is plays an important role in South Africa biowarfare counter-proliferation and emerging disease monitoring is the National Institute for Communicable Diseases NICD serves an analogous function to the Center for Disease Control in the United States. It is also the main infectious disease lab for coping with natural or man-made emergencies for the entire African continent. The NICD has several laboratories, including a BL-4 lab and will be the primary national laboratory if the country ever goes to war.

Today the NICD has three primary goals: 1) infectious disease surveillance, 2) research related to surveillance, and 3) capacity building (Dr Schoub, Interview, June 24, 2003). Much like the Center for Disease Control, the NICD is responsible for national surveillance of all infectious diseases within South Africa. However, the NICD is also responsible for surveillance throughout Africa (see NICD.ac.za for more details). If a patient in Central Africa comes down with an Ebola or Marburg virus, he or she will be transported to a South Africa public hospital for management. The NICD has an excellent track record of success and it is unusual for health care workers to become infected when dealing with patients with the most dangerous infectious diseases. NICD staff was able to successfully handling suspected cases of SARS during the past year by using an extensive informal network of continents. NICD staff have been collecting a library of specimens of infectious diseases found in Africa since the 1970s and has one of the few BL4 laboratory facilities in South Africa.

The headquarters and laboratory facilities of the National Institute for Communicable Diseases (NICD), located in a suburb of Johannesburg, evolved from several earlier organizations and programs. The earliest forerunner was a March of Dimes drive against polio in the 1940s. This drive evolved into a permanent non-governmental organization that focused on polio modalities, diagnosis, and vaccines for polio. In 1976, after the Marburg virus outbreak, the South African government recognized the need for a national centralized resource center and took over the NGO and rename it the National Institute of Virology. The laboratories and headquarters of the former NGO were transferred to the SA Dept. of Health (see NIV.ac.za).

[17] Several interviewees claim that the National Institute for Communicable Diseases has the only Biosafety level 4 laboratory in the country. However, one microbiologist at NICD reported that she thought the South African Police Forensic lab had one. She also noted that as a scientists working in public health, she does not know anything about the medical and laboratory facilities currently being used by the South African National Defense Force (SANDF).

The mission of the organization has expanded to cover research on all human viruses. In 2002 several different organizations were merged under a new governance structure as part of a rationalization and cost-cutting effort (Interview with Dr. Schoub, Director of NICD; www.NICD,ac.za). The National Institute for Communicable Diseases (NICD) currently includes several public sector medical laboratory services, a new National Health Laboratory Service (NHLS) formerly the South African Institute for Medical Research (SAIMR), and various provincial laboratories. NICD replaces the former National Institute for Virology (NIV) and the microbiology, parasitology and entomology laboratories from the former SAIMR.[18]

Managing infectious disease outbreaks: The importance of informal networks and a large library of infectious disease samples

Since the NICD provides surveillance for the entire continent, the organization is experienced in establishing structures if none exist to provide the capacity for early warning. The lab staff of 10 people, including only 4 scientists, recently was able to quickly identify outbreaks of yellow fever in Sudan, the Democratic Republic of the Congo, and the Seychelles. One NICD scientist attributed their high rate of success in rapidly diagnosing diseases in part to a library that has collected specimens of infectious diseases in Africa since 1976!

The NICD was recently involved in the global effort to identify and manage suspected cases of SARS infection. NICD has also tested specimens from over 1,000 anthrax scares, and is developing teleconference capabilities so that all of the provinces in South Africa had early warning capabilities. No national network capability for early working exists today but NICD is working to develop one in the near term. Because of the limited capacities in South Africa and other African countries, NICD often relies on an informal, inter-personal network. The director, Dr. Scrub, felt this informal network was important to NICD's ability to respond quickly to the recent SARS epidemic. NICD was able to quickly confirm that not one of the 150 suspected cases was an actual SARS infection. The general assessment of NICD scientists is that the informal structures and collaborations that were already in place with colleagues in Hong Kong worked reasonably well throughout the crisis.

The NICD professional staff believes that they learned importance lessons from their recent experiences dealing with the SARS outbreak crisis. While the NICD normally completes one or two diagnostic tests per day, they were able to handle many more daily tests during the SARS crisis. NICD microbiologists felt that an even more important requirement for coping with an infectious disease epidemic is the ability to establishment of a good sorting system. NICD personnel already had taught "who to call" worldwide during a health crisis from their experiences dealing with a recent influenza outbreak. They found that efficient sorting of the hundreds of phone calls received during the SARS crisis was extremely important to ensure that their limited resources were not overwhelmed. Throughout the crisis they managed to run hundreds of necessary tests in their one lab while also responding to queries from throughout the continent about SARS and other infectious diseases (Interviews with NICD personnel, June 24, 2003).

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[18] As noted above, the National Institute of Virology (NIV) closed down most if its vaccine facilities because vaccine technology, including its yellow fever and polio vaccine manufacturing facilities. It continues to produce snake venom antidote and falls under the jurisdiction of the national Dept. of Health.

NICD Collaborations with NIH, USAMRIID, and WHO

Dr. Schoub, the Executive Director at the NICD, emphasized that the organization has lots of collaboration with the US National Institute of Health (NIH). Dr. Bob Swanepoel, the senior scientist in charge of Special Pathogens, is currently collaborating with NIH researchers on emerging infectious disease research. Current collaborations build upon earlier collaborations, including Joint South African-US field teams from Ft. Detrick/USAMRIID who worked together in the Congo throughout the 1970s and 1980s to diagnosis and clinically manage early outbreaks of Marburg and Ebola viruses among US peace corp. workers. Since that time, personnel from the two governments have often cooperated in efforts to collect and analyze data on infectious diseases in South Africa and the wider region.

NICD personnel are also involved in several ongoing international early warning projects, including the recent World Health Organization (WHO) project to develop a Special Outbreak Response Network. NICD lab personnel use the WHO web-based Outbreak Verification Data Base of Suspected Diseases extensively. NICD lab personnel also use PROMED online email alerts as an additional tool. However, since PROMED is not peer reviewed, it is felt to be less useful than the WHO database on suspected infectious disease outbreaks. NICD personnel also work closely with the South African Dept. of Health's Communicable Disease Outbreak Unit headed by Dr. Chabalulu Hlupeka.

NICD Research

NICD supports a variety of research programs including: research on a HIV/AID vaccine using a virus as a vector; research on special pathogens from animal and insect viruses such as hemorrhagic fever, ebola virus, the Rift Valley fever, and rabies; research on clinical viruses such as polio, rubella, and influenza; and microbiological research on infections including anthrax, plague, malaria, typhoid, and cholera. NICD is also working on vaccines for a variety of common infections including meningitis and pneumonia; and epidemiological research on the characterization of viruses and infected community's behaviors. In several lines of research on vaccines, NICD researchers are seeking to use indigenous South African plants as a source of vaccines. For example, one project is using finger printing to sequence genome data for trees that are thought to be a promising source of vaccines for Rift Valley Fever.

NICD's diagnostic focus is on developing rapid diagnostic capabilities. The lab has micoarrays and one of the only BSL-4 labs on the continent used to diagnose infectious diseases in humans.[19] Dr. Schub emphasized that the NICD lab facilities were behind those available in the US. They had only one small micro array that used finger stick specimens. However, he noted that NICD was moving to improve current laboratory diagnostic equipment. He also emphasized that NICD microbiologists had been able to develop special diagnostic techniques for viral pathogens and HIV AIDS. In the area of bioinformatics computer modelling one NICD researcher, Dr. Bessclaar, has developed an advanced influenza program. NICD uses a dedicated LINUX computer primarily because it is less expensive than Windows.

[19] As noted previously, infectious disease scientists working in the public health sector do not know how many BSL-4 laboratories there are in the country. While there may be additional BSL-4 labs in South Africa, the BSL-4 lab at the NICD is the only one in the country used to diagnose infectious diseases in people. Several individuals I interviewed were under the impression that NICD had the only BSL-4 lab in the country. Dr. Schub said he was not sure how many there were as he was under the impression that the South African Police Forensic Lab either had or was in the process of developing a BSL-4 facility. He noted that there might be one or two additional BSL-4 labs in the country but he was confidant that the facilities at NICD were the only ones in the country used for human health diagnoses of infectious diseases in humans.

Assessment: An infectious disease and War on Terrorism resource

The strategic importance of NICD as the central diagnostic center in Africa for infectious diseases is obvious. Long-term professionals such as Dr. Schoub and his associate, Dr. Bob Swanepoel, are among the most knowledgeable medical researchers of infectious diseases in Africa today. They and other NICD colleagues have a great deal of experience working to diagnose and clinically manage old and emerging infectious disease using ad hoc communication systems. The increased number of emerging diseases being brought into the United States in recent years suggests the importance of increasing collaboration with the NICD in the areas of disease surveillance and targeted vaccine research.

Under certain circumstances NICD personnel could provide useful information about human activities related to possible biowarfare activities. Dr. Schoub came to the institute in the late 1970s. Dr. Swanepoel is a highly effective and credible microbiologist today in part because he is one of the few microbiologists working for the apartheid government who was not involved in secret biowarfare research. Their combined past experiences, contacts, and reputation provides them with access to a great deal of information about what is going on with infectious diseases in South Africa and throughout the continent. Dr. Swanepoel, for example, is on an International Board for Biodefense and frequently consults with governments from such diverse areas of the world as Africa and Eastern Europe. Because the NICD also has one of the most sophisticated BSL-4 labs in the developing world, researchers at the NICD have extensive contacts throughout the developing world. The BSL-4 at NICD also routinely analyzes samples sent from as far way as Pakistan.

The contacts and data available at NICD are likely to become more important in the future as more people gain competency in biotechnology that can be used for military or terror purposes. While the NICD has no formal interactions with private companies, actors in the private sector are expected to provide "good will statutory notification" when they are working with infectious agents or encounter possible infectious disease agents. As yet, there is no enforcement mechanism in place to monitor the activities of biotechnology start-up companies or to hold them accountable in terms of notification requirements or norms. Thus, for many reasons it may be a wise practice to support new cooperative activities with NICD in the areas of early warning, diagnostic procedures, and research on infectious diseases with relevant DOD entities, in addition to continuing ongoing collaborations with researchers at NIH. Much like the Medical Research Council's overall view of which dangerous pathogens are moving around South Africa, the NICD has the best overall picture of reported medical research involving human subjects and the state of progress on develop new vaccines and drug delivery systems throughout the continent.

1.3c Future issues related to medical R&D and the movement of medical materials in South Africa

Given the changes in leadership and professional practices at the MCC, the MRC, and all public universities and research institutes in South Africa, it is difficult to see how South Africa could be used for illegal medical research activities today or in the foreseeable future without someone in the organization leaking information about covert activities. While medical trials conducted at spring clinics run by the SA National Medical Service (SANMS) remain outside the jurisdiction of the MCC today, leadership changes in the reorganized and integrated SA National Medical Service (SANMS) operate under the same norms and professional practices that guide their counterparts in civilian health today. These changes make a recurrence of illegal medical research at SANMS institutions highly unlikely. Instead, current ethical issues related to the many medical clinical trails in South Africa today revolve around the appropriateness of testing first world drugs on a population that is unlikely to be able to afford to use these drugs in the near-

term future. Another concern for senior MRC officials are unsubstantiated rumors that there are illegal human tissue exports occurring in South Africa today.[20]

1.4 Potential Proliferation Threats: Private Biotechnology start-up companies and Technikons

One of the most interesting trends in South Africa's biotechnology today is the fact that a number of very small private biotechnology start-up companies, along with a few more well-established but small companies, are renting laboratory bench space at under utilized "Technikons" that were built during apartheid as showcase technical colleges for academically gifted black South Africans. Several new biotech companies are currently working on a "shoe string budget" at out-of the way scientific laboratories at Technikons. Three biotechnology companies who are doing some of the most innovative biotechnology research in the country today, Shimoda, MeyerZall, and Biological Control Products, are profiled in detail in Section II. From a proliferation perspective, the fact that there are already a dozen or so such companies suggest that this may be the type of private entity that will proliferate in the future in South Africa. This trend may make it much more difficult to monitor and control civilian biotechnology R&D activities in South Africa and other developing countries in the future. No one knows yet how many private start-up biotechnology companies there are in South Africa. Estimates range from 6-to-50. The national audit currently underway aims to identify and describe all research being conducted at biotechnology units in the public and private sector. However, the biotechnology audit being financed by the Dept. of Science and Technology also relies on voluntary self-reports.

Currently, the number of biotechnology start-up companies and university programs that train graduate students in how to use sophisticated biotechnology techniques in South Africa is very small. Most biotechnology researchers know each other and are aware of what other groups are doing, at least in general terms. This trend is likely to change as the size of the scientific pool of researchers trained and experiences with using sophisticated biotechnology techniques grows. It may become extremely difficult, if not impossible to monitor all of these groups in the future. South Africa today is well on its way to having a small but growing number of well-trained researchers chasing too few well-paying jobs. If this trend is replicated in other developing countries it could become extremely difficult to monitor trends in civilian biotechnology, especially since many of these companies have fewer than 10 employees and most are choosing to remain private rather than public companies.

The former Project Coast scientist, Dr. Daan Goosen, who is currently working with Peter Smits, runs one of these new start-up biotechnology companies. The two scientists are renting lab space at the Pretoria Technikon to work on special vaccines for small animals. According to Dr. Goosen, his group consists of five people, including students who were working on several new generation vaccines including an antigenic vaccine that uses common Ecoli bacteria. They are also developing a "designer" or specially targeted animal vaccines and are working on a system to identify bacteria molecular sub-classifications. Goosen recently reported that while the computer they use is very small, they have DNA finger printing equipment in their molecular lab. This equipment is enough to allow them to develop designer vaccines. The approach they are using is based on analyzing one common element in the DNA fingerprint that is used to produce a targeted vaccine (Interview, June 26, 2003). However, the picture painted by professional

[20] Dr. Tony Mbewe made this latter point during a phone interview on July 31, 2003. Much of the information about the MCC and the increase in clinical tests in South Africa was based on information from the MCC website and from interviews with the following individuals: Dr. Tony Mbewe, (Interviews Dr. Mbewe, MRC; Dr. O. Muller, Managing Director, QdotPharma, his associate, and Dr. Gevers,).

acquaintances is bleaker. Dr. Hans Jager, who worked for years with Dr. Goosen at Onderstepoort, said that Goosen's lab had no working products so far to sell. Dr. Jager had also heard that Dr. Goosen's group's only commercial contract with the European Union for animal experiments had run out (Dr. Hans Jager, Interview, July 1, 2003).

1.5 Gaps in Regulatory process of Animal and Human Health Research

Overlapping jurisdiction created by legislation means that several different committees are working to regulate the potential dual use of biotechnology. For example, both the Department of Health and NPC issue export control licenses that are suppose to be obtained for all imports. Several institutes that have BL3 or BL4 laboratories are regulated by different agencies. While the Dept. of Agriculture oversees the Foot and Mouth Institute and Plant Protection Unit at Roodeplaat, the NPC and animal regulatory agencies oversee Onderstepoort. One of the principle concerns of Dr. Southern, the current biotech industry representative on the NPC, is the lack of coordination between the Department of Agriculture and the NPC. Given the role of DOA in granting import licenses and responsibility for inspecting food exports, including exports that have been produced with genetic modified technologies, he felt that more coordination between the two organizations is crucial. Although the DOA has been invited to become a member of the NPC, it doesn't yet have a representative on the Council. This means that representatives from the two organizations, especially from the Directorate of Genetic Resources at DOA and the NPC do not speak with each other or coordinate their actions. Given the current lack of staff and funding at both public agencies, it is doubtful that this gap will be filled in the near term.

Research that involves humans subjects is regulated by several different government agencies. A license is needed from the Medical Research Council for all agents brought into or out of medical facilities for research. Even human cells that are to be imported or exported from the country are not suppose to be moved without first obtaining a license. While such an extensive control system may be impressive on paper, the regulatory resources needed to police such a system are not in place. The limited staff and magnitude of the task results in many gaps in the NPC inspection regime. There is little formal interaction between the Non-Proliferation Council and the Medical Control Council. Thus, it remains unknown how much is moving through South Africa without the required legal licenses.

Despite the extensive amount of legislation in place there are also several gaps in the public regulatory processes in South Africa. Currently, there are no laws governing animal experimentation in South Africa. This means that effective monitoring is difficult because the number of animals that suffer and die in laboratories each year is unknown, and no official information exists on what institutions do animal experiments and what experiments are conducted. It also enables overseas scientists, institutions and companies to conduct research locally in order to escape stricter laws in their own countries. Perhaps the most vigorous actors who serve a watchdog function for possible proliferation threats involving animals are non-governmental public interests groups such as South Africans for the Abolition of Vivisection (SAAV).

Another legislative gap related to animals involves animal vaccines. Poultry vaccines that are produced in-house by major private animal vaccine companies do not have to be registered with the government due to a loophole in Act 35. The largest private animal vaccine manufacturer in South Africa, Avimune, works with the Manufacturing Association. While the activities of this company are of interest to the NPC, no inspections or formal reporting requirements have taken place (Interviews, Dr. Jager, Director of R&D, Avimune Pty Ltd., July 1 and Dr. Southern, July 8, 2003).

These gaps in the regulatory process make covert biological research much easier to sustain. Today, there is also little communication between bureaucrats tasked with registering animal feed and remedies in the Ministry of Agriculture and members of the NPC. A lack of interaction is also apparent between NPC

representatives and staffers and employees of SAGENE, the regulatory body responsible for overseeing genetic modified organisms (GMOs). Much like the gulf found in other countries, little work has been conducted to date in South Africa to bridge the gap between regulators involved in lab safety, biosafety, national security, intelligence, or among diplomats negotiating arms control treaties and those working on the Biodiversity Treaty. There were no formal lines of communication with Defense or Intelligence and thus, no consideration of the possibility that plant fungi, for example, might be used as a weapon.

Finally, there have been no inspections to date by the NPC at some of the most sophisticated facilities for R&D of plants, animal research, human health, and manufacturing processes and products that use sophisticated biotechnology methodologies that are located at research universities and at laboratory facilities at Technikons that are located throughout the country. There are sophisticated labs at Witswaterand University, University of Cape Town and several other research universities where sophisticated proteomics and genomic research is being conducted. According to NPC members, there are numerous BL3 laboratories and at least 20 additional fermenters that still need to be inspected. The bioincubator at CSIR in Pretoria and several sophisticated labs run by the Agricultural Research Council (ARC) will probably not be inspected because they are under the jurisdiction of the Dept. of Agriculture, the MRC, MCC, or other regulatory bodies. Even though the NPC has the authority to inspect many of these facilities, they currently lack the staff to do so. Dr. Southern expects that the negotiations required before each site inspection are likely to be lengthy and take several years to complete. The South African experience with domestic inspections suggests that international non-proliferation approaches that are based primarily on domestic inspection and regulation will be slow, costly and incomplete.

1.6 Shared beliefs and perceptions of threat

Although the gaps in the regulatory process of South Africa and the unknown number of small, private biotech companies in South Africa may be viewed as potential proliferation concerns in the United States, these concerns are not shared by most South Africans. Few South Africans today believe that biological pathogens constitute a major security threat. In fact, it is difficult to find South Africans who are particularly worried about security threats stemming from bioterrorism. Threat perceptions among South African researchers and government officials are very different than those found today in the United States about the serious threat posed by the use of biological agents in future terrorist attacks.

Majority View: "BW is not a threat"

Most interviewees asked the question of whether, "There is a threat from the dual use of biological agents and biotechnologies in South Africa?" The majority view was a resounding "No" to the idea that biotechnology R&D would serve as a cover for covert biowarfare research. Many South African researchers do not view biological agents or technologies as serious security threats. In fact, several of the interviewees said that they didn't even want to think about the question since secret biowarfare programs were a thing of the past that ended with the demise of apartheid.

For most respondents, the magnitude of threats posed by the increasing HIV/AIDS infection rate, along with other infectious diseases, makes the question of biowarfare threats irrelevant for most of the scientists interviewed for this study. Instead, most interviewees believe that new biological processes and products made possible by genetic engineering are important because they offer ways to improve existing health and economic problems in developing countries. While not all of the respondents would agree, many echoed Prof. Gevers, head of the South African National Academy of Science, assessment that "South

Africans (today) are pacifistic" and that " the ethos have changed as HIV and TB have increased" (Interview, July 10, 2003).

The devastating impact of infectious diseases throughout the region during the post-apartheid era also explain why so much of the current sophisticated research using biotechnology in South Africa is focused on vaccine development and related health products. As Dr. Scrub noted during our interview:

> "the most pressing issues pertain to how to improve current methods for detecting and coping with new infectious diseases. These new diseases increase the importance of developing newer, targeted vaccines" (Interview, June 24, 2003).

Dr. Paterson, the Chief Operating Officer of the DST echoed a widely expressed view that one of the most important features of the South African system that operates as a very real constraint on secret biowarfare R&D in either the pubic or private sector today; "South Africa is a highly connected system…if there is a start-up company somewhere conducting dual use research people will know." Currently, the pool of scientists, engineers, and researchers who are trained in using sophisticated biotechnology is so small that everyone seems to know every one else involved in biotechnology research and in general terms what type of research others are doing. The small size of the research pool also means that many members of the biotechnology community tend to view each other either as competitors, or increasingly with the implementation of the Biotechnology Strategy, as collaborators in research or efforts to establish new start-up biotechnology companies. Just how small the pool is indicated by the fact that the new biotechnology funds are having difficulties identifying neutral experts in the country to serve as peer reviewer for Innovation Funds and Biological Research and Analysis grant proposals!

Instead, DST officials are focused on ensuring that substances considered prescribed substances under the Weapons of Mass Destruction Act do not enter or leave the country, and that public and private facilities capable of producing large amounts of biological agents eventually come under national safeguards. The emphasis on national controls of any institution that can produce large quantities of chemical or biological agents is why Onderstepoort, the public-private animal research unit from which several Project Coast veterinarians were recruited during the 1980s, was the first site subject to inspection by the Non-Proliferation Council.

One wonders when viewing the magnitude of the control tasks and the limited resources of the NPC if these non-proliferation tasks can be completed. Mr. Arthur Boettcher, Deputy Director: Non-Proliferation & Space diplomatically voices similar concerns when he noted that with only two people working on CBW inspections and verification of imports and exports, the most important constraint facing the NPC administrative staff was time and limited resources (Interview, June 25, 2003). This situation is unlikely to change in the near future. The country faces more pressing problems, and much of the urgency in establishing verification protocols and implementing inspections of sites working with biological agents dissipated after the BW Treaty Verification Protocol talks collapsed in 2002.

The importance of societal constraints

Faced with scarce resources, the Dept. of Science and Industry senior government officials, and members of the wider scientific community are relying heavily on societal constraints to control covert CBW research in South Africa. There was near unanimous agreement among the South African interviewees that large-scale production of biological agents for a mass attack was infeasible today because of the policies of the current government and because most members of South African society support the

non-proliferation policies of the current government. Most of the scientists interviewed felt that any rumors regarding questionable uses of existing facilities would be quickly reported to authorities. A vigorous investigative press and several non-governmental watchdog groups are also important actors in South Africa who monitor alleged secret or unethical behavior of individuals and organizations with the same vigor that they used to learn more about South Africa's former nuclear weapons programs during the closing days of apartheid. The main difference today is that these groups have access to more information, have fewer political restrictions on what they can write and say about public officials, and can now easily communicate worldwide on the web. Thus, most individuals in the South Africa elite assume that suspicious activities by the government and by private individuals will be quickly publicized once they become known. Others, such as Dr. Peterson, head of DST, recognizes the possibility that biowarfare agents can be produced anywhere. He noted during our interview that, "we won't know what someone is doing in their garage in the suburbs" (June 25, 2005).

Minority Views

Terrorists will use "what's on hand"

Most interviewees, who were willing to contemplate a terrorist threat that terrorists, agreed that terrorists would be most likely to use easily obtainable pathogens such as botulinum rather than genetically engineered or enhanced agents. Most of the individuals queried about what agents terrorists would be most likely to use said that viruses such as smallpox or hemorrhagic fever would not be used because they were difficult to obtain. In the case of hemorrhagic fevers, one microbiologist observed that the outbreaks haven't lasted that long in the past in Africa and so the supply of the virus is very limited. Of those queried, most interviewees also agreed that anthrax was a more likely candidate since it is so pervasive throughout the region. A few felt that HIV could also be used as a biological weapon. Others, such as Dr. Hans G. Jager, the former Director of R&D at Onderstepoort and current senior scientists at Avimune, identified an animal pathogen as his pathogen of choice if he were going to engage in terrorist acts in South Africa would be hoof and mouth disease.

View the threat as a continuum – Crude-through-sophisticated and "Get all labs on standard"

Dr. Daan Goosen, a former Project Coast scientists (Interview, June 26, 2003), emphasized the importance of viewing the nature of biowarfare threats along a continuum ranging from sophisticated genetically modified pathogens, including the use of vaccines as a biowarfare weapon, to crude approaches such as using foot and mouth disease. For Goosen, "open transparency and freedom of information are the key way to control biowarfare threats" at the scientific level. Dr. Goosen's specific recommendation for monitoring the civilian biotechnology sector is to "get more countries in the developing world on international laboratory standards" used by the United States, the EU, and the OECD. South Africa has a similar body that regulates Good Laboratory Practices (GLP) called the South African National Accreditation Service. This accreditation body certifies GLP based on an internationally recognized standard. The GLP systems of accreditation and regulation are based on "good faith" voluntary compliance so any lab that is not in compliance would be easier to spot once more countries adopted existing standards of accreditation and certification. Although this approach would not address the problem of the "lab in the suburbs" or the bush, Goosen felt that an emphasis on accrediting laboratories was a more productive approach than the current focus on having international bodies disclosing to other international bodies. Goosen's suggestion seems particularly well suited for South Africa given the large number of small,

private start-up biotechnology companies laboratory, including his own, who are setting up lab facilities in rented facilities at several different Technikons around the country.

Gaps and lack of communication among different bureaucratic regulators within and across nation-states

The difficulties encountered by the South African NPC in monitoring the movement of controlled agents, issuing permits, conducting on-site inspections and the gaps in their domain of enforcement exemplify the types of problems that should be expected in efforts to implement non-proliferation measures based on monitoring the flow of controlled substances in other countries in the developing world. The lack of cooperation and communication between agencies such as the NPC and MRC creates a serious gap.

The current regulatory divide found in South Africa and the lack of communication among government professionals concerned with laboratory safety, biosafety, security, intelligence, and biodiversity is universal. However, this in-depth case study of South Africa, a developing country with a narrow but advanced scientific sector, provides some vivid illustrations of why current practices need to change. The recent concern with aflatoxins as a terrorist weapon illustrate even better why lines of communications must be built across agencies that rarely are involved in national or homeland security.

1.7 Future Issues – Biotechnology, proliferation and emerging issues in developing countries

Several emerging issues proved difficult ones to research. There are numerous rumors floating around about an outflow of illegal human, animal, and plant tissues from South Africa. Several senior regulators and researchers reported that they hear these stories but don't have details or evidence of such trafficking. No interviewee had enough information to determine whether these rumors are true, who is involved in the illegal trade, or even the extent to which illegal trafficking in human and animal tissues is occurring in South Africa today.

Section II

Civilian Biotechnology Trends in South Africa

2.0 Factors fueling the decline of South Africa's biotech capacities during the 1990s

Since 1994, the African National Congress (ANC)-dominated government has spent a great deal of time and energy reorganizing bureaucracies and implementing a privatization process of government run-parastatal organizations that was started in some sectors by the former government in the early 1990s. Today, many former parastatals are private companies or are run as public-private partnerships. For most former parastatals, the government remains the most important customer for most of the new corporations and the state owned public-private partnerships are strongly encouraged and expected to earn more of their increase in the future from private sources.

The country's science councils were also reorganized during the 1990s. CSIR units today are expected to become self-supporting and spin-off profitable private corporations. Similar organizational changes are underway at all of the units of the Agricultural Research Council (ARC). Other ARC institutes, in addition to Ondestepoort and the Animal and Hoof Institute, are important actors in civilian research because they conduct experiments and animal studies using genetic modification and other biotechnology techniques.

Reforms in South Africa have been costly. In recent years the government has struggled to privatize and promote a growing private sector while also coping with the costly dislocations caused by rising incidences of HIV-AIDS and other infectious diseases. Funds to fight the AIDS pandemic compete for funds going to other needs. One activity that was consistently cut on an annual basis throughout the 1990s was funding for basic scientific research and science education. By the end of the 1990s cumulative cuts in funds available for basic research in several disciplines were endangering the world-class status of South Africa's major research institutions (Interview with Prof. Jennifer Thompson, University of Cape Town, July 10, 2003).

Two additional trends that adversely effected government efforts to promote biotechnology R&D in South Africa occurred during the years leading up to and immediately after the political transition in 1994. Many foreign businesses left South Africa. Among the large foreign and national large corporations that remained in operation in South Africa, most eliminated their R&D divisions that were not making a profit by the end of the decade. In several cases, this meant that companies totally shut down or sold off biotechnology research units or corporations. Dow Chemical sold their business interests in South Africa. Many large South African companies also sold their biotechnology divisions. For example, the South African company, AECI, well known for their explosive products, sold their plant and gene libraries to the CSIR Undoubtedly, this corporation trend fueled further emigration among science professionals. Many white scientists felt that they had no future in the new South Africa. Others wanted to stay but couldn't find a job. These trends had a direct, adverse impact on the amount of biotechnology R&D conducted in both academic and industrial institutes across several related fields.

The result is that the country's capacity to do sophisticated biotechnology R&D had eroded significantly by the end of the 1990s. The result of the steep decline in large corporate involvement in biotechnology. According to Dr. Southern, the private sector representative on the NPC, at least 40 or more quantitative biotechnology scientists have left the University of Stellenbosch. Among these departures are two world class plant and wine bioresearches, Dr. Pretorius Sakkie and Dr. Freekie Botha, formerly affiliated with Stellenbosch. Dr. Sakkie, formerly at the Wine Institute of Stellenbosch emigrated to Australia. Dr. Botha left academia to work for the Sugar Institute in Durban.

An interesting very recent trend may be a modest reversal of emigration patterns among South African scientists, especially junior researchers and those in the area of health science research. Several younger South Africa scientists, who use sophisticated biotechnologies in their research, wanted to return home to make a contribution to finding a vaccine or other medicines to help cope with the HIV/AIDS pandemic, or other infectious disease. Many of these recent graduates were able to come home because they were offered post-doctorate research positions that were funded by private, foreign donors. Whether the new returnees will stay remains uncertain because most of the new positions are being paid for from short-term (i.e., 3-5 years) external grants from foreign donors that may not be renewed in future years.

The loss of large corporate support for biotechnology research and development created a void in terms of generating new products and jobs in biotechnology. A desire to stimulate new commercial R&D discoveries and jobs were the primary reasons why the current government undertook new financial obligations associated with a new national biotechnology strategy in 2001. After years of studying the problem, government officials reached the conclusion that a new initiative was needed to stop the deterioration of human and physical capacities that the country needed to conduct world-class biotechnology research. The government was also concerned about the larger crisis in science education in South Africa and trade issues of common concern to countries throughout the developing world. Since many of the same macro trends influence the state of biotechnology R&D throughout the developing world, several of the problems and issues that South Africa officials and researchers are wrestling with today approximate those found in other developing world.

2.1 Evolution of South Africa's Biotechnology Strategy

The national biotechnology initiative is part of a wider South Africa's development strategy. South Africa politicians and senior bureaucrats are trying to develop a strategy that embodies a "third approach to capitalism." This third approach envisions a larger role for government in helping to create new corporations and jobs than is recommended in neo-Keynesians capitalism. The third approach assumes that a government will be able to provide more support for indigenous entrepreneurs, attack new foreign investment and thus stimulate economic growth while also working to achieve sustainable development and poverty reduction goals. This strategic context is important to understand because it explains why the South African government has invested large sums of money to promote costly high tech R&D that create only a few jobs.

Most biotechnology R&D in South Africa currently uses first or second generation technology. Applications of these technologies are found primarily in the production of wine and beer using first-generation technology or in genetic engineering research that used genomic data.[21] Several South African industries and researchers began to explore the use of biotechnology in a number of fields throughout the 1990s (i.e., in heath science, biodiversity, and mining). According to one mid-level Dept. of Science and Technology government analyst, "although South Africa was not preeminent in most fields, it had developed an extensive pool of expertise in commercial biotechnology R&D" (Mr. A. Kudlinski, DST, Interview, June 25, 2003).

About five years ago the Dept. of Science and Technology (DST) initiated a series of roundtables and study groups using the British Foresight model.[22] The planning process started with a plenary session on genetic modified organism (GMOs), sponsored by the Agriculture Research Council. This session was followed by discussions in several working groups and geographical projects (Mr. Andre Kudlinski, Dept. of Trade and industry, June 25, 2003). Most researchers using biotechnology in commercial or university research were involved in one or more of these workshops. The development model adopted in South Africa was based on the generic model of promoting biotechnology by using a government-university-corporate partnership. The South African government formally adopted the Brazilian model because it recognized the need for the national government to play a large role. This approach emphasizes the importance of the government playing a role in stimulating new companies and jobs. This approach fits with the views of many involved in the South African planning process (Kate Aspden, phone interview, June 17, 2003).

Initially, the government emphasized getting the appropriate legislation in place. The early emphasis on legislation was fueled by the lack of legislation throughout most African countries and a recognition among National Biotechnology planners that the lack of legislation would become an increasingly important limiting factor in promoting commercial biotechnology (Interview with Prof. Mark Laing, July 1, 2003). The concern was also fueled by growing opposition to genetically modified (GM)

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[21] According to Mr. Andre Kudlinski, beer breweries in South Africa have not wanted to be associated with the government efforts to develop a new biotechnology initiative since the mid-1990s (Interview, June 25, 2003).

[22] The U.K government provided funds and technical assistance to produce several Foresight reports from this process. See for Example: Health: Foresight National Research and Technology Foresight Project. Dept. of Arts, Culture, Science and Technology, Pretoria, South Africa, 1999 (ISBN 0 7970-3797-7).

seeds and agricultural products in Zambia, Malawi, and Zimbabwe. Government planners and commercial farmers in several countries in Southern Africa are increasingly concerned that local agricultural exports may be barred from the European Community if GM seeds from the United States or elsewhere are widely used.

In contrast to the government and public perception of genetically modified (GM) seeds in Zambia, Malawi, and to a lesser extent Zimbabwe, there is little official opposition to the use of genetically modified organism (GMO) in South Africa, Botswana, Lesotho or Swaziland. In fact, when Lesotho faced widespread drought, US AID created a GM seed that was widely used and credited with helping to reduce the impact of the drought. One reason given by interviewees for the very different reception in South Africa when compared to other countries in the region is that most of the agricultural initiatives that involved GM seeds in the country were introduced through university programs. All of these programs have conducted careful fieldwork prior to introducing GM seeds into local communities (Thomson, Interview, July 10, 2003; see also Thomson, 2001).

Given the regional political environment, South Africa officials and researchers decided the country had to take a proactive approach to issues related to genetic modified organism (GMOs) and biotechnology generally to prevent future trade barriers among SADCC countries and with European Union trade partners. Currently there are serious concerns among government planners in all governments in the region about whether European Union policies related to GM agricultural imports would exclude certain products from the region.

DST's Biotechnology Report and the White Paper on Biotechnology

The Dept. of Science and Technology (DST) issued a report in 2001 that outlined the current state of the R&D in South Africa and what needed to be done to re-invigorate research in applied biotechnology research (see http://www.dst.gov.za/programmes/biodiversity/biotechstrategy.pdf). The White Paper acknowledged that several South African producers had worldwide reputations in the application of biotechnology in their fields, i.e., in mining, industrial clean-up and wine fermentation. The report went on to emphasize that most sectors of the South African economy lagged one or two decades behind R&D trends in economically advanced countries. A central theme of the document was the need for a more coordinated government response and the establishment of geographical centers designed to promote further existing biotechnology activities in each region in manufacturing, biochemistry, pharmaceutical and medical research, and agriculture. The importance of developing high-tech sectors and job creation as part of the national plan was also stressed. The document also emphasized the need to develop modern economic human and physical capacity throughout Africa in order to meet the African Union's New African Partnership for African Development (NAPAD) goal of finding a third approach to promoting both economic growth and poverty reduction throughout the continent (Dr. Adi Paterson, Paterson, June 25, 2003).

The Innovation Fund

The report recommended expanding efforts to re-invigorate R&D biotechnology beyond activities funded by the Innovation Fund. The Innovation Fund provided modest, i.e., US$100,000-to-200, 000 grants, to eight-to-ten collaborative projects to commercialize products that were near completion annually. The goal of the Fund was to help revitalize the process of translating basic research into viable biotechnology commercial endeavors. Key considerations in awarding these grants include whether a project will be profitable, create exports, and generate new jobs downstream.

Just how important job creation has been as a factor is illustrated by DST's willingness to support the construction of the one and only commercial biotechnology plant in South Africa, an amino acid (lysine) plant outside of Durban. DST continued to fund the project for several years while costly start-up issues were solved. It took several years before the lysine plant to develop enough niche markets to earn a profit. DST also supported two related chemical endeavors. One project, initiated by SASOL, is designed to produce fuel more efficiently. The Biological Business unit R&D effort is running another project. The idea behind the funding is to develop enough manufacturing capacity to create demand to take advantage of the region's ability to produce cheap energy and sugar products.

Researchers interviewed for this study, especially academics, were much more positive about Innovation Grants than traditional grant sources (i.e., the National Research Council) or newly established BRIC funds (see below). According to one university researcher the Innovation Funds had "transformed South African science by encouraging collaboration across universities who had previously been like a pack of dogs fighting over very scarce bones"(Laing, Interview, July 1, 2003). Other interviewees were enthusiastic about the program's ability to provide funding to bridge the gap between basic research discovery and commercialization. While a few researchers felt the government had unrealistic expectations about what could be accomplished in a 3-to-5 year period, most researchers familiar with or recipients of Innovation Funds were reasonably positive about the ability of the program to accomplish its goal of stimulating biotechnology applications.

This positive assessment contrasts sharply with the majority academic view of the paltry amounts of public funds available from the National Research Council. Many academic researchers also complained about cumbersome requirements, delays, and unrealistic expectations associated with the new BRICS grant competition (see below). One researcher, who wishes to remain anonymous, went so far as to characterize the new BRIC funding initiative as the "valley of death."

A common complaint heard from academics about both Innovation and BRIC funding is that the funds are only available for commercialization of basic research. Most academic researchers believe the government's current strategy creates an unrealistic distinction and disconnect between fundamental (or basic) and applied research. University researchers also complained about the unrealistic assumptions related to the length of times and resources required to translate basic research insights into profitable product. Nearly all of the academic researchers interviewed for this study wondered aloud about what would happen in three-to-five years when the existing basic research innovations and investments have been exhausted. New innovations at research universities are hampered by limited amounts of funds for basic research. In the absence of adequate funds for basic research, most academics have been competing and using funds earmarked for commercialization to cover basic research costs as well. Nearly all of the academic researchers interviewed for this study felt that it was unfortunate that the Innovation Funds were being phased out as new funds that will be awarded by BRICS administrator come on line.

Biotechnology Incubators

The Department of Science and Technology has supported the establishment of several biotechnology incubators dedicated to helping biotechnology start-up companies get started. Biotechnology incubators are public funded offices established to help businesses interested in translating promising biological research insights into commercial endeavors. Today there are eight incubators located in major cities throughout South Africa.

Many academic researchers are critical of the effectiveness of the incubators as a resource to help them translate basic research into commercial ventures. According to Prof. M. Wingfield, Director of the Forest and Agricultural Biotechnology Institute (FABI) at the University of Pretoria, an advisory

Management Committee that included academics, students, and staff set up the EcoliBio office in Pretoria very quickly over a six-week period. The incubator was originally envisioned as the third official Biological Research and Innovation Center, PlantBio. Towards that end of the planning process, researchers at the University of Pretoria and CSIR worked together using funds from a three-year, three million Rand Innovation grant to commercialize a new form of fungi as an additive to blue cheese. However, Dr. M. Wingfield's experience was that the use of Innovation Fund for the project tended to marginalize academic research. The problem from his perspective is that it is impossible to do innovative research that leads to a commercial product in plants and animals in a three-year time frame. Although Dr. M. Wingfield feels that there is a place for the services offered by incubators at universities, his view is that to date the government has failed to support the technical platforms at a level necessary to support basic research. A related problem voiced repeatedly by academic researchers is the paucity of biotechnology companies and jobs generated by government initiatives. The limited number of jobs makes it nearly impossible for the incubators to fulfill one of their most important intended purposes, job creation (Interview, June 26, 2003).

The Biotechnology Strategy

In 2001 the South African government tried to bring the several different biotechnology programs into a coherent strategy designed to stimulate the growth of a private biotechnology sector. The national biotechnology strategy was introduced in June 2001 as an effort to promote a partnership among government, universities, and the private sector. The three official goals of the Biotechnology Initiative are to promote: 1) innovation and commercialization, 2) increased cooperation among business, academic and research communities, and 3) promote greater public understanding of biotechnology. The initial funding priorities of the new government focused on commercial applications in industry, agriculture and health sectors. The government is also emphasizing research that uses proteomics and genomic. To facilitate more advanced 4th generation research, the government also supports a South African National Bioinformatics Initiative (SANBI). The goal of SANBI is to connect researchers at Research University and other research units into a national computer network whose central node will be at the University of Western Cape where the country's only Cray super computer is located (see Section 2.2b for more details about SANBI).

2.2 Overview: Civilian Biotechnology Applications in South Africa

There are about 500 biotechnology projects spread over seven sectors in South Africa. A public advocacy group, AfricaBio, estimates that these projects involve 110 groups drawn from academic and research institutes and about 45 private companies ("South Africa: Status and Future prospects of Biotechnology, " 2003). The medical and pharmaceutical sector is the largest sector employing state-of-the-art biotechnology and the one that receives the most funding in recent years. The plant sector is the second largest. Commercialization of plants is projected to be an area of rapid growth as demand increases for products made from South Africa's unique biodiversity increases. Industrial and animal husbandry applications have been widely employed with the largest concentration of biotechnology firms and divisions in Guetang and Kwazulu-Natal Province.

An important change over the last decade is that most multinational corporations have spun-off their biotechnology divisions or closed down operations in South Africa. New, small biotechnology companies are being formed in an attempt to fill the void and to develop new applications in the chemical, forestry, animal and human health vaccine and pharmaceutical industries. Microbicides are being used on a small scale in both mining and environmental sectors. All sectors depend heavily on imported biotechnology

applications, external investors, and international collaborations. Several very small biotechnology companies have been formed in recent years to commercialize unique intellectual properties and patents developed by South African researchers. Much like the defense industry, South African biotechnology companies and units are exhibiting success in developing biotechnology applications for niche markets. No one really knows how many biotechnology startup companies there are in South Africa today. The Ecoli Incubator at the Council of Science and Industrial Research was completing the first survey of all companies and research units using biotechnology was still being compiled in mid-2003.

2.2.a Geographic Locations of Biotechnology Companies

South African biotech start-up companies are located throughout the country with the largest number located in Guetang province. Major areas employing biotechnology include agriculture, animal and human health, forestry, mining and industry. Most new companies are spin-offs from basic research conducted at research universities (i.e., University of Witswaterand, University of Pretoria, Rands Africans University) or research institutes (i.e., CSIR, Ondestepoort, NICD, National Health Laboratories).

The Western Cape is the area of greatest growth in new biotechnology companies and where many biotechnology start-up companies are expected to locate in the future. The Westgro Fact Sheet (2002) claims that 60 percent of all biotechnology start-ups who recently sought funding were located in the Western Cape. Newer companies involved in medical research (i.e., BioVac, Shimoda, Ribctech, Synexa, Baylabs and Genec) are developing alongside older firms such as Meyer Zall. Newer food production companies in the region (i.e., Abakor, Irivin & Johnson, Swift Micro Laboratories.) are developing alongside established companies such as SA Breweries. WineTech and other companies have joined government and university sponsored research programs to improve wine production. Ninety percent of this production takes place in the Western Cape.

The BioEden Initiative, which is trying to establish a private biotechnology hub around George in the Eastern Cape, claims that there are about 12 biotechnology start-up companies in the region. There has been a steady increase in the volume of business being conducted by private companies who run commercial trials using human subjects to test new drugs, vaccines and other medical devices in both the Western and Eastern Cape.

Another major cluster of companies surround Durban (i.e., the Sugar Research Institute, the Lysine Plant, Durban there is another cluster along the industrial highways leading into and out of Durban. Biological Control Products (PCP) is located in a strip industrial center off the highway between Durban and Pietermaritzburg. Small firms like BCP co-exist alongside older biotech R&D programs affiliated with the sugar industry and the government sponsored Lysine plant. Several dozen relative new biotechnology firms are scattered throughout the country. Most of these companies have chosen to remain private and will not be listed on the Johannesburg Stock Exchange. Most of these companies promise to be profitable and have already attracted outside investment. Many of these small biotechnology firms also have close ties with US government agencies (i.e., USAID, NIH, etc). However, there are a handful or maybe even several dozen other South Africa biotech start-up companies that little is known about, in part because they are located in the northern part of the Western Cape, Northern Province, northern Kwazulu-Natal, or the Orange Free State.

2.2b State-of-the-Art Human Health Research

Several lines of human health research underway in South Africa today may be relevant for understanding types of research and biotechnology capabilities that are likely to be undertaken in

developing countries in the future. Table 3 summarizes three lines of research that illustrate how sophisticated some of the human health research projects in South Africa are today. These three lines of research are all collaborative international projects involving researchers in several developed countries. The activities of BioVac, a recently established private company designed to produce state vaccines are also summarized. The trend of establishing private companies to produce a range of vaccines for public health is one that is growing throughout the more affluent countries in the developing world.

DNA metabolism, mutations, and the physiology of tuberculosis

Dr. Valerie Mizrahi, Research Professor at the National Health Lab Service, leads this research effort in South Africa. The project focuses on how a tuberculosis bacterium deals with DNA damage and developing genetic methods to identify new drug targets for tuberculosis. By studying the basic bacterial physiology of tuberculosis and exploring properties of the organism. She and her associates now understand how DNA metabolism copies, introduces and repairs mutations. Since many mutations that kill organisms are introduced into the DNA, this line of research is viewed as critical for increasing our understanding of the mechanisms that can be used for coping with drug resistance.

Dr. Mizrahi's group has found that the bacteria that causes tuberculosis acquires a mutation in the chromosome that makes it resistant to drugs. They have identified a novel protein that plays a key role in developing drug resistance (see Boshoff, et al, 2001). This mechanism has been studied in animal models and is now viewed as a novel way to cope with drug resistant tuberculosis. The research originated at NIAID in Rockville, Maryland and current collaborators on the genetic methods project include researchers in US, the United Kingdom and Australia. The UK Wellcome Trust and Howard Hughes Foundation, along with the US and South African governments have supported this line of research.

Until recently, Dr. Mizrahi was hampered by the lack of sophisticated micro array equipment and had to rely on colleagues at the University of Cape Town and in Australia to produce microchips. However, her lab at University of Witswaterand has recently acquired the first DNA micro array in South Africa and she expects to be able to answer some very fundamental questions about drug resistant development on tuberculosis causing bacteria (Phone interview, July 31, 2003).

Epistemology of HIV-1 Molecular epidemiology in Kwazulu-Natal

Many medical researchers in South Africa today are working to understand better the epidemiology of the HIV-1 as a first step in developing more effective drugs and vaccines. MRC and several private and public external sponsors supports HIV-AIDS research at all of the South Africa research universities. At the University of Natal-Durban, HIV-AIDS research is supervised by Professor Sharon Cassol. Dr. Cassol is affiliated with the African Center for Health and Population Studies and the Molecular Bioinformatics Unit at Nelson Mandela School in Durban. Prof. Carol's research was frequently cited by interviewees as one of the most promising lines of research on HIV-1 in South Africa today. Researcher groups working the HIV-1 Molecular epidemiology in Kwazulu-Natal and most other medical researchers working in HIV-AIDS have access to BL3 laboratories.

Plant and Edible Vaccines

The MRC has also funded several individual projects on edible vaccines. One project repeatedly cited by the experts interviewed for this study was research conducted by Prof. Rybicki at the University of Cape Town until it was stopped for safety reasons. There are also several on-going novel research projects

underway studying how plants can be used as a medium to grow vaccine epitope. What is unique about several of the projects in the Western Cape of South Africa is that they are exploring substances in indigenous plants, particular those unique to the Western Cape and other regions of South Africa. The goal is to find substances that can be used for new drugs. This is an area where many South African researchers feel they have a comparative advantage in the field of drug discovery if they can protect their research from being taken over by foreign interests. Some of the proposed projects are designed to exploit indigenous plants for medicinal purposes that involved genetic modification were not been funded due to concerns about the use of genetic modification technology in plants (Interviews with Profs. Laing and Thompson).[23] In the Guetang area, the National Institute for Communicable Diseases (NICD) is also pursuing several lines of research using indigenous South African plants to explore the potential use for vaccine delivery or new drug compounds. One project is using finger printing to sequence genome data for trees that are thought to be a promising source of drug therapy for Rift Valley Fever.

Genome sequences of variability in HIV using bioinformatics

One of the most-publicized lines of recent medical research in South Africa is an international effort conducted by a multi-national team of researchers. Two of the better known members of this line of research are two sisters who contributed research for a combination of vaccines that are scheduled to start field trials soon in the US and South Africa. Dr. Carolyn Williamson worked on one vaccine, called AlphaVax that is manufactured by a US biotechnology firm. The MCC is expected to give the green light for both the AlphaVax and two other AIDS vaccines soon. One vaccine was developed by pharmaceutical company Merck and the other by the International AIDS Vaccine Initiative. Dr. Carolyn Williamson works at the University of Cape Town in conjunction with Dr. van Rensburg and other colleagues located at the Institute of Plants in the United States. She also works with researchers at several other institutes in the US and Europe.

Dr. Carolyn Williamson's unique contribution to the project was to focus on the basic genome sequences of variability in the more common HIV C strain found in South Africa, China and other areas of the developing world using bioinformatics techniques. Dr. Williamson isolated and characterized the antiviral and found a single cell antiviral vaccine in vitro that may form the basis of a HIV vaccine for genital virus infectious diseases (Morris, et. al. 2000). The candidate vaccine developed from Dr. Williamson research is causing a great deal of excitement since it may prevent the strain of HIV found in 80% of cases diagnosed in South Africa. A team of mostly women, including Dr. Carolyn Williamson and her sister Anna-Lise, developed the vaccine. The researcher's preliminary data indicate that their new vaccine, when used with other vaccines in a combination called Prime Boost, may block the AIDS virus.

Table 3: South African Medical Research

Research Topic	Research Leader	International Partners
-DNA metabolism, mutations & tuberculosis to ID new drug targets	-Dr. Valerie Mizrahi Director, National Health Lab Services & Wits Univ.	Original: NIAID, Rockville, MD Current collaborations: US, UK & Australia Funded by UK Welcome Trust Howard Hughes Foundation, USG, & SAF

[23] A good POC for this line of research is Prof. Steyn, Microbiology Department at the University of Cape Town (see Appendix A for contact details).

-Epistemology HIV-1 -Molecular epistemology	-Dr. Sharon Cassol Welcome Trust Fellow, Director, African Center for Health and Population Studies, Medical School University of Natal-Durban	-Dr. van Rensburg, Institute of Plants, US -Welcome Trust, SAG, Bill & Malinda Gates Foundation, several other international funders
-Plants & edible vaccines using plants for expression -NICD, many others exploring use Cape bio-diversity	-Prof. Rybicki Dept. of Molecular/Cell Biology, UCT -Use plants for HIV vaccine expression. Project stopped due to safety issues	-See Prof. M. Laing or Thomson for more details (contact information in Appendix A)
-Genome sequences of variability in HIV using bioinformatics -AlphaVax -Prime Boost HIV/AIDS cocktail	-Dr. Carolyn Williamson University of Cape Town Institute of Infectious Diseases & Molecular Medicine (with sister Dr. Anna-Lise Williamson)	-South African Aids Vaccine Initiative (funded by SAG, US Army, Walter Reed, NIAID, a lab in the UK, other African countries) -Several other international foundations -AlphaVax is manufactured in US
-BioVac Institute -Produces 7 child vaccines -R&D drug delivery using plants for virus formation HIV & TB	-Dr. Woolf Katz R&D Director, BioVac Institute, Cape Town, South Africa	-Formed from South African Vaccine Institute (SVI) -Major investors include SAG Dept. of Health, Haber (Cuban biotech Co.), VacIntel (UK -Working with Sequella, MeyerZall -Customers include SAG, UNICEF, UKG, Bill & Melinda Gates Foundation

2.3 New Government Applied Research and Vaccine Production Activities

South Africa AIDS Vaccine Initiative (SAAVI)

The UCT vaccine initiative undertaken by Carolyn Williamson, her sister, several other researchers at UCT and nearly every other major South African health research institute, are funded by the South African AIDS Vaccine Initiative (SAAVI). The government, the SA electricity supplier, Eskom, and several foreign donors are funding the SAAVI initiative. The South African AIDS Vaccine Initiative was established in 1999 as a lead program of the Medical Research Council to develop an affordable and effective HIV vaccine for southern Africa. SAAVI funds various SA research groups testing AIDS vaccines. Speaking on the 6th World AIDS Vaccine Day, May 18 2003, SAAVI director Dr Tim Tucker noted that, “SAAVI has developed into a sophisticated national biotechnology” (www.saavi.org.za).

The role of outside money in funding sophisticated SAAVI research

While the amount of funds available for basic biological science research from traditional national research sources (i.e., from the National Research Council) remains small, there has been a huge influx of money available for vaccine discovery from South African industry and from private foreign donors.

Several other vaccine discovery research initiatives are currently being supported at most major universities including the University of Witswaterand, University of Cape Town, and Stellenbosch. Nearly all of these programs are being run in conjunction with efforts to attract young medical researchers back to South Africa.

For example, at the University of Cape Town much of the newer research is being funded by five-year Wellcome trust grants based in the United Kingdom. According to Prof. Gevers, President of the Academy of Science of South Africa (ASSAF) and a former Vice-Provost at UCT, the influx of outside research money has allowed distinguished universities, such as UCT to reverse trends of top researchers leaving the country (Interview, July 10, 2003). Skeptics wonder how this group of bright young researchers who have returned to South Africa will be paid when the Welcome Trust and other foundation grants run out. Some institutions are having trouble absorbing the amounts of money from foreign donors and are using some of the money to build modern new facilities. The new UCT medical complex currently under construction is a good example of an institution that has benefited from the influx of international funds for HIV-AIDS research.

The huge amounts of funds from outside donors, such as Melinda and Bill Gates, has had a transformational impact on what many South African researchers are studying. Nearly all-successful medical research today is international projects fueled by outside funds. The focus of much of this research is on clinical applications. The best-known example of the "internationalization" of South African research is the South African AIDS Vaccine Initiative (www.saavi.org.za) supported by national organizations, such as MRC, along with a number of national and foreign private and public institutions. The first clinical trials of a collaborative US-South Africa-UK HIV-AIDS vaccine research project finally started in August 2003 in the US and South Africa.

The SAAVI initiative is a collaborative effort involving researchers at AlphaVac, a private company, and the U.S. Army Medical Research Lab at the Dept. of Defense Walter Reed hospital, a lab in the UK, and several African countries. Phase 1 trials for the first AIDS vaccine candidate started in the US and South Africa in early August 2003. The national sites in South Africa are located in Johannesburg and Durban. AlphaVac in the United States is conducting simultaneous trials. In addition to South African government funding, the major South African utility company, Eskom, and the National Institute of Allergy and Infectious Diseases (NIAID) are also contributing to the project that will test an AlphaVac replica Vector (ARVTM) clade C candidate HIV-1 vaccine. What makes this project so notable is that it is the first HIV vaccine trial to be approved in South Africa and the first in the world to test a subtype C vaccine (see http://www.mrc.za.za/pressreleases/ for more details).

There are eight other SAAVI backed projects going on at this time looking at novel candidates for HIV-AIDS vaccines. Some of this vaccine development research involves biotechnology techniques. Most of this research is being conducted with partners in Kenya, Uganda, West Africa, and as far away as India (Tony Mbewe interview, July 31, 2003). Large amounts of funds from MRC and outside donors are also going towards clinical research and to build treatment facilities.

South Africa's experiences in the area of developing new HIV/AIDS vaccines and in many other areas of health research illustrate the reality that nearly all successful collaboration in the area of world health are collaborative international undertakings. From a non-proliferation perspective this trend is encouraging as it suggest that medical health research will be one area where it will be difficult for developing countries, who are integrated into the modern economic world system, to maintain a secret biological warfare agents research program. However, from the perspective of several South African researchers, the international collaborative nature of health research risks creating new divides in international relations. Dr. Valerie Mizrahi, for example, worries that the limited amount of funds that South African researchers can contribute to international project means that South African researchers will

increasingly be treated as junior partners who are dependent on funds from NIH, the Wellcome Trust or other sources even though they are making major contributions to collaborative international research projects (Phone interview, July 31, 2003).

Applied Vaccine Research and Production in South Africa

Coping with HIV-AIDS and job creation are two powerful factors fuelling public support for vaccine research. Substantial amounts of MRC funds, along with funds from outside investors, are also being invested in efforts to bring down the cost of vaccines and drugs by building domestic capacity to produce generic drugs and vaccines. The perception among many academic basic human health researchers in South Africa today interviewed for this project is that too many government-sponsored efforts to commercialise vaccines and to expand drug production facilities are taking funds away from more basic research initiatives.

Even if the new emphasis on commercialisation is hurting basic science research, the South African government is likely to continue supporting efforts to develop the capacity to produce vaccines and drugs domestically because this is an important SAG priority. In 1996, South Africa imported drugs worth 250, 000 rand (Interview with Mr. Kudlinski, Acting Director; Chemical and Allied Industries, DTI, June 25, 2003).). Locally produced vaccines for common childhood diseases, HIV-AIDS, and other infectious diseases are viewed as a way to reduce these foreign exchange expenditures while also providing revenue and jobs upstream.

One needs to understand the importance of these two government imperatives---coping with HIV/AIDS and job creation---in order to understand several recent SA government initiatives. In the past, two state owned institutions, the South Africa Vaccine Plant at Edenval and the South Africa Vaccine Institute (SVI) manufactured vaccines (Interview with Dr. Schoub, NICD, and June 24, 2003). The National Institute of Virology continues to operate as a parastatal under the jurisdiction of the Department of Health. In the early 1990s the NIV closed down it's yellow fever and polio vaccine manufacturing facilities. Vaccine technology had far outpaced the capabilities of the facilities which had not changed much since the Institute's early days. While the government closed the SAVP production facility in recent years, it also spent US$10 million dollars to keep the SVI open by funding a new project designed to revitalize the production facilities. The SVI facility currently produces an antiserum snake vaccine and employs 10 people.

BioVac: A Public-Private Company

The government has invested heavily in a new public-private company, BioVac that was spun-off from the South African Vaccine Institute (SVI) in order to produce a number of common vaccines. The major investors in BioVac to date is the national Dept of Health, a Cuban biotechnology entity, Haber, and a local South African partner financed BioVac. VacIntel in the United Kingdom is a technical partner but owns no equity shares.

The mission of the public-private partnership is to help create a private pharmaceutical industry in South Africa by producing good quality, safe, and affordable vaccines for African diseases. Biovac is manufacturing a wide range of vaccines. The main product currently is a combination vaccine for children that include vaccines for seven or eight childhood diseases in one shot (i.e., polio, measles, BCG). BioVac is working with Sequella on this project in an effort to keep the production costs down. The national Dept. of Health is BioVac's main customer. UNICEF also plans to buys a large number of vaccines from BioVac for selling to countries that are in the category of borderline poor. Other BioVac customers are the British Commonwealth Office, and the Bill and Melinda Gates Foundation.

Biovac plans to complete for a market share of the demand for African vaccines with the three-to-four leading multinational vaccine manufacturers who operate in Africa (e.g., Avantis Pasteur, Smith-Kline-Beecham). BioVac has an agreement with the state to procure vaccines from multinational pharmaceutical companies for 15 years. According to Dr. Katz, Director of Research at BioVac, "there is a large market for vaccines in Africa but no money to pay for the vaccines" (Interview, July 8, 2003).

BioVac believes it can compete with the large multinationals for markets in Africa because their production costs are lower and there is only one other institute on the continent producing African vaccines. The other African institute is Vacera, an Egyptian institute closely affiliated with GlaxoSmith Kline. Biovac also plans to purchase vaccines in bulk and repackage them overseas. However, few details are available about this joint venture at this time because negotiations with a private company are still underway.

BioVac is researching rabies vaccines previously conducted at the State Vaccine Institute (SVI) and working on a project designed to produce an inexpensive vaccine antigen. BioVac also manufactures a tuberculosis vaccine that was developed at SVI. BioVac is also involved in several joint ventures. BioVac is working with one of the major TB units funded by the Gates Foundation. BioVac's role will be to scale up and prepare the clinical trial material. Both University at Cape Town and Stellenbosch are prepared to conduct clinical trials of any biological (i.e. protein) materials developed at Biovac for potential use in vaccine development. BioVac is also working on vaccine drug delivery system using plant viruses for malaria, HIV, and TB. Clinical trials using the plant production system are scheduled to start soon and will be run by the Clinical Research Center in Pretoria.

Another line of BioVac's research focuses on producing an ingredient that will be an additive to facilitate drug absorption with one of the more successful private biotech firms in South Africa, MeyerZall (see Section II). BioVac owns shares in the new technology. Finally. BioVac has a joint venture with the Heber Institute in Cuba.

"Enough smallpox vaccine to vaccinate half of all residents in Africa"

There is a large amount of smallpox vaccine at BioVac's R&D and storage facilities outside Cape Town. The vaccine was manufactured prior to the 1972 World Health ban. According to Dr. Katz, the Director of Research at BioVac. Dr. Katz produced the 40 million doses of smallpox vaccine, which "if diluted to 1:10 it could provide enough vaccine to inoculate half of all Africans" (Interview, July 8, 2003). Dr Katz said he used "old dead sheep" technology to make the vaccine because smallpox was still endemic to the region in the 1980s. When questioned about the general understanding that smallpox had been eradicated from the region, Dr. Katz noted that there was still an occasional case and that he had studied how to make it in 1964 at the State Vaccine Institute. He said the government was already producing it when the old South African Defense Force troops started fighting on the border with Angola against regular Cuban troops started in the 1970s. The former government wanted to have a large amount of the small pox vaccine on hand just in smallpox was used in Angola.

According to Dr. Katz, the current government thinks it's a good idea to keep it around because there is no system in place or money to pay for an alternative vaccine using live animals. It would take more than two years to develop and produce an alternate smallpox vaccine. The South African government probably couldn't afford to pay for a new vaccine since it would cost US$ 2-to-3 dollars versus the 2 cent per dose cost Katz's on hand store cost. The annual storage costs are rand R20, 000 and Katz claims it is a very stable vaccine and is degrading at a slow rate. He tested it six months ago and it was still good. Katz said that US Embassy personnel know about the vaccine and had spoken with him about the stockpile.

However, they told him the US was not interested in it because it was produced by very old methods of production.

A Therapeutic Substance Regulatory Committee regulates the vaccine. Physical security of the vaccine is loose. The BioVac facility, which also houses live animal and tissue cultures, is in an urban area just off the major freeway to Cape Town. The only physical barrier around the facility is a slender fence. While there may be more guards, only one security guard was visible at a main gate entrance near the office complex of the BioVac facility.

2.4 Key Characteristics of South Africa's Civilian Biotechnology Sectors: Small, inter-connected, with lots of international collaborations

When the Biotechnology Initiative was announced in 2001 South Africa had a small but growing biotech private sector, a world-class group of biotech researchers in several fields, including agriculture, medicine, and genetic research, and a system of state-supported research labs managed by the Council for Science and Industrial Relations (CSIR). The most important characteristics of South Africa's biotechnology R&D activities across all sectors are that most new biotechnology startup companies are very small activities. Nearly all of the recent private biotechnology corporate ventures are efforts by small groups of researchers and MPAs who specialize in commercialization of intellectual property. Most of the intellectual property and patents were developed at universities during an earlier period before universities in South Africa started insisting on a share of the intellectual ownership and commercial profits.[24] Thus, many of the successful biotechnology R&D in South Africa today are the result of international collaborations that involved South African researchers contributing to a multi-national collaborative research project. A few examples will illustrate each of these characteristics.

2.4a Small Size

One of the most striking characteristics of South Africa's civilian biotechnology sectors is how few companies and research institutes are using state-of-the-art biotechnology. In the area of human health there are only about five successful quality private biotechnology companies in South Africa. Animal vaccine manufacturing is dominated by a few leading manufacturers who operate in South Africa. Only one of these companies, the recently privatized BioVac company, is a South African company. As discussed in Section 1, BioVac is a public-private partnership rather than a private company. Its revenues depend upon an exclusive contract to supply the South African Health Department to produce several essential vaccines for the next 15 years. BioVac also has several large contracts with UN-affiliated organizations. Several foreign partners, including the Cuban-based Heber Corporation, VacIntel in the UK, and several technical partners who have no equity investment financed it. In the area of animal vaccine, Onderstepoort continues to be a major producer of animal vaccines although it appears to be losing or have lost its competitive edge as a major sponsor of cutting edge research. In the area of poultry vaccines, a private company, Avimune, now dominates in terms of supporting sophisticated R&D.

[24] In the past, South Africa universities did not routinely claim Intellectual Property rights. This practice started to change about a decade ago. However, before universities started to claim licensing rights and a percentage of royalties many researchers left with the Intellectual Property rights they had developed while working at a university (Interview, Mark Fyvie, Cape BioTech, July 7, 2003).

2.4b Highly inter-connected and increasingly integrated within universities and across institutions

Resource shortages in academia throughout the last decade forced many academic departments involved in using biotechnology to merge at most research universities in South Africa. Thus, much of the state-of-the art basic research related to biotechnology today is taking place in recently merged departments that have combined faculty and laboratory facilities in related fields such as microbiology, bio-chemistry, molecular cell biology, and applied biotechnology.

2.4c South African National Bioinformatics Initiative (SANBI)

The most significant area of cooperation and inter-university integration of research resources related to biotechnology in South Africa is the establishment of the South African National Biotechnology Initiative (SANBI) that is nearly completed. SANBI is a consortium of researchers at universities and public-private institutes who are developing an integrated computer network tied to the only Cray supercomputer in South Africa at the University of the Western Cape (UWC). When this integrated system is in place, researchers at major universities and some other research institutes will be able to conduct 4th generation proteonomics and genomics research using the UWC computer, state-of-the-art software, and shared gene libraries and databases.

Dr. Winston Hide, a bioinformatics, has a world-class reputation for his work isolating the gene for hereditary blindness. He returned to South Africa after working in commercial pharmaceutical research and research sponsored by the U.S. Department of Energy in the mid-1990s. Dr. Hide started SANBI with only one post-doctorate. The bioinformatics program at UWC now has five doctoral students training in bioinformatics. Dr. Hide is the principle architect for the national bioinformatics research center and a magnet who attacks world-class researchers to UWC (Interview with Renfrew Christie, Director of Research, UWC, July 8, 2003).

In April 1996 researchers who support the master plan concept behind SANBI at several universities (i.e., Pretoria and Rhodes in South Africa, University of Pisa in Italy) came together to develop a SANBI plan to build a central computing center at the University of Western Cape (UWC) since UWC has the only Cray supercomputer in South Africa. The immediate goal is to link important local resource nodes in structural bioinformatics at University of Rhodes, Pretoria, several other universities and CSIR to the UWC supercomputer. A new Africa Center for Gene Therapy (ACGT) has been established at CSIR in Pretoria to ensure that industrial researchers affiliated with CSIR will also have access to the national network. Today, SANBI's mission has three components: 1) research, 2 training, including short services courses in bioinformations and 3) to serve as the national server (NCBI) for universities and other research entities that will be connected to the SANBI computer network. A national computer network is nearing completion in South Africa. The next task will be to implement the longer-term goal of providing access to researchers throughout the African continent!

Currently, an important constraint on fourth generation bioinformatics research in South Africa and throughout the developing world today is limited access to wide enough band width, high speed computers, and data bases needed to do sophisticated informatics research.[25] More SANBI-type consortiums throughout the developing world will go a long way to eliminating an important barrier to conducting

[25] The POC for more details about the computer capabilities of SANBI and details about how band width serves as a major constraint for bioinformatics research in South Africa and throughout the developing world is: Caspir Schutter, SANBI, University of Western Cape, Bellville, South Africa, cschutte@icon.co.za.

sophisticated genetic research for civilian or military purposes. If present trends continue, similar SANBI-like consortiums can be expected to spring up throughout the developing world within 5-to-10 years

2.4d Lots of International Collaborations

During the first decade after apartheid, South Africa reintegrated into global economic and political systems. Most South African biotechnology researchers have extensive interactions with colleagues in other countries and are seeking additional collaborative research projects abroad. The international collaborative nature of the South African biotechnology sector is one of its most distinguishing characteristics. Most recent successful R&D projects that have used sophisticated biotechnology have been international collaborations. The international collaborative nature of most successful, sophisticated biotechnology R&D in South Africa has unintended but important non-proliferation benefits. This characteristic of state-of-the-art biotechnology research in the country is the main reason why there is little cause for concern about sophisticated research being used for dual purposes.

The international collaborative nature of research projects stems from the fact that most research scientists are trained at western universities. Many South African researchers receive training and have worked in several countries. Much like their counter-parts in the developed world, South African scientists also have a global network of colleagues with similar interests. They have similar real-time access to recent R&D results throughout the developed world. Consequently. it is hardly surprising to find that nearly all members of the South African biotechnology R&D community also belong to a larger global scientific community.

A few examples illustrate the highly globalize nature of biotechnology activities in South Africa today across a number of fields (See Table 4). For example, Professor Jennifer Thomson, University of Cape Town, has established an international reputation for her work in developing drought-resistant maize. She is also involved in international collaborative research, has written a best selling book on the genetic revolution (Thomson, 2002), and has served as a consultant on biotech issues for such international luminaries as UN Secretary General Koki Anan.

Many people were surprised to learn in May 2003 to learn that the first cloned cow on the African continent had been born. However, the research project, conducted in South Africa by a small team of three principle researchers is typical of many smaller scale research projects that occur in South Africa. In this case, two South African veterinarian researchers worked with a visiting colleague from the Danish Agricultural Research Institute. This small-scale collaboration, based on personal links established by individual researchers in South Africa, and one or a few researchers in other countries, is the most typical pattern of collaboration in South Africa biological and biotechnology research today (Dr. Mark Winfield, University of Pretoria, Plant Biotechnology, Agriculture, Crops, and Forests, phone interview June 13, 2003). Similar small group international collaborations are also found throughout African and other parts of the developing world.

The methodology used to clone the first cow in South Africa is so simple and cheap that it may signal a new era of affordable cloning for researchers in developing countries. The technique, called "homemade cloning," to create genetically identical copies of animals is much cheaper and simpler than existing methods. According to Michael Bishop, ex-president of Infigen, a cattle-cloning company in Wisconsin, "It's a huge step towards roboticising the whole process." The inventors of the new technique claim that personnel can be quickly trained to use the method. Currently, researchers are exploring the feasibility of using the technique to clone endangered species (Westphal, 2002).

Future applications of the new cloning method may soon create exceptions to the more general trend in biotechnology applications in South Africa. To date most applications that did not involve

extensive international collaboration used either first or second generation techniques and approximated trends R&D trends found in developed countries 10-to-15 years ago. Nearly all of the successful, more sophisticated research found in South Africa today involves international collaborations. Several examples of sophisticated international, medical collaboration were detailed in Section 2.2. The cutting edge research by Dr. Mizrahi and the Williamson sisters with their international collaborators is today the most typical pattern of the most sophisticated research in all fields of science. Sophisticated biotechnology research related to both animal and human vaccines is also taking place at the premier research universities including: Pretoria, Rhodes, Stellenbosch, University of Cape Town, University of Free State, University of Witswaterand.

A key common ingredient to the success of these recent medical breakthroughs has been the availability of large sums of money from various foreign donors, such as the Bill and Melinda Gates Foundation, the Wellcome Trusts and the National Institute of Health (NIH). One of the more interesting findings of this research was the confirmation that NIH had identified and has become involved in most the larger scale medical research projects that are currently underway in South Africa.

2.5 Biological Regional Innovation Centers (BRICS)

The first prong of the biotechnology strategy is to establish three Biotechnology Regional Innovation Centers (BRICS) to facilitate the growth of private sector biotechnology firms. To date, two of the three centers have already opened. The Guetang BRIC is called **BioPAD**, while the BRIC in the Western Cape is called **CapeBio**. A third center, **PlantBio** is in the final phase of planning and should be opened soon in Kwazulu-Natal.

One of the most important activities of the BRICS is to award start-up grants to projects that can become self-sustaining private corporations within three years. The idea is to provide seed money to promote the expansion of the biotechnology private sector quickly in order to reduce the amount of public involvement needed to finance biotechnology start-up companies in the future. The initial commitment to fund the new biotechnology initiative through the BRICS was a total of US$50 million (equivalent to 400 million rands). The funds were to be allocated over a three-year period. This amount represented a significant higher level of funding

Table 4: Technology examples of South African Research & Development

Technology Examples	Applications	Sponsor	POC
Genetically modified seeds and plants (drought-resistant)	Agriculture (i.e, maize, cassava, & Resurrection Plant)	Rockefeller Foundation South Africa Maize Trust	Prof. Jennifer A. Thomson Dept. of Molecular and Cell Biology, UCT, South Africa
Handmade Animal Cloning	Agricultural applications (cow)	Endangered Wildlife Trust, South Africa in collaboration with Danish Institute of Science	Paul Bartels, Endangered Wildlife, Johannesburg, SA or Gabor Vajta, Danish Institute of Agricultural Sciences, Tjele, Denmark or Ian Lewis, Cooperative

			Research Center, Innovative Dairy Products, Australia
Tuberculosis Research	Medical	SAG & USG (NAID) collaborations in US,UK, Australia, UK Welcome Trust & Howard Hughs Foundation	Dr. Mizrahi, Director, National Health Lab Services & Witswa-terrands University, South Africa
HIV vaccine cocktails	Medical treatment	SAG (SAAVI), USG UK and African investors AlphaVax in US manu-facturing AIDS vaccine	Dr. Carolyn & Anna-Lise Williamson
Drug delivery systems	-Topical delivery of drugs & vaccines (Emzaloid,Meyer-Zall) -Capsivirus intra-cell-ular (Shimoda)	Private investors	Dr. Johan Erasmus, Meyer-Zall, George, SA Greg Gilbert, CEO, Shimoda, Plettenberg Bay, SA

to support biotechnology R&D than in the past and reflects the reality that biotechnology industry is a research-intensive industry where 40% -to- 50% of revenue usually goes towards R&D. However, the amount actually allocated for the initiative has been substantially lower. Cape Biotech and BioPAD were allocated 12.5 million each while PlantBio is scheduled to receive a total of US$ 7 million.[26]

With limited resources the BRICs are being asked to fund projects and micro-to-small/medium size bioventure startup companies that may be too risky to be able to attract soft capital venture capital fund. These same projects are expected to create a large number of jobs. Originally there was also supposed to be a division of labor among the three BRICs that reflected the different commercial biotechnology activities that predominate in Guetang, KwaZulu-Natal and the Western Cape. The Johannesburg area BRIC, BioPAD was supposes to focus on bioprocess, veterinarian, and environmental and industrial acuities, especially in the areas where CSIR had active R&D programs. Cape Biotech located in Cape Town and designed to service the Western Cape, was to specialize in bioprocess and human health. The proposed Durban BRIC would emphasis agriculture, especially biotechnology uses related to plants and commercial agricultural products. In practice, there is a great deal of overlap among the areas that will be supported by the three BRICS. The overlap between CapeBio and the proposed PlantBio appears to be nearly 100 per cent!

Each BRIC is suppose to fund projects at varying stages of development. The common requirement is that a project must be commercialized, produce revenue, and generate a profit within three years. This requirement has caused a great deal of angst amongst basic researchers, especially in academia, who believe that the BRIC funding is imposing unrealistic requirements on basic research efforts. Since each BRIC is at a different stage of development, the activities of the two operating BRICs, BioPAD and CapeBio, both of which evolved from existing biotechnology incubators, and the planned activities of PlantBio are described separately below.

2.5a Cape Biotech

[26] This amount was reduced over the last year from a projected $12 million.

Cape Biotech came into existence as a non-profit organization in mid-2002. Cape Biotech is located in an office building complex that houses several related business, including the Western Cape's regional biotechnology incubator, Acron. Although there are more biotechnology companies in the Guetang region, the Western Cape hub, located around Cape Town hosts a great deal of sophisticated biotechnology R&D. Key sectors in the region involved in biotechnology R&D include medicine, environmental, pharmaceutical, and industrial, genomic and bioinformatics (der Derian, 2003). According to one analysts, about 60% of all South African biotechnology start-up companies who have approached venture capitalists for funding are located in the Western Cape region, many predict that this region, and to a lesser extent the Garden Route, will be the main hubs for high technology biotechnology R&D in the future (Gavin Goldblatt, phone interview, June 16, 2003).

Exhibit 1 lists the 15 short-listed projects recently chosen by peer review for possible funding from CapeBio. Approximately three quarters of the Cape Bio-tech's projects relate to human health. The other projects on the list are projects related to industrial bioprocessing. The projects cover a broad range of activities from developing compounds from indigenous plants to methods to optimize the production of beer and wine. Dr. Mark Fyvie. CEO of Cape Bio, expects his entity to fund seven or eight of these projects. In addition to awarding grants, Cape Biotech has also invested in three systems in an effort to expand the R&D biotechnology capacity of the region. This investment included a platform technology, a genome center to facilitate tissue analysis, and a facility to manufacture vaccines or pharmaceuticals.

Dr. Mark Fyvie, recently noted, "Our mission is to develop and promote Biotechnology capacity in the Western Cape that will create significant and sustainable economic and social value for South Africa" (Interview, July 7, 2003). Cape Biotech aims to do this by helping the Western Cape become a world-class biotechnology hub. He feels this is a feasible aim "because of the world-class research community in the region with well-developed expertise in medical, environmental, pharmaceutical, industrial and agricultural biotechnology, as well as in bioinformatics and genomic" (Interview, July 7, 2003).

2.5b BioPAD

BioPAD also came into existence in 2002. BioPAD initially operated out of the offices of the EGoliBio Incubator at CSIR but recently moved to a suit of offices near CSIR in Pretoria. Exhibit 2 lists the program for the First Annual Bio/Chemtek conference. The close links between the University of Pretoria and CSIR are evident from this program. The composition of members of the Board of Trustees for BioPAD indicates a very close relationship between BioPAD and CSIR as well. The head of the Bio/Chetek Division of CSIR is the head of the Board. Other members are drawn from CSIR and leading academic centers and departments throughout the country involved in commercial biotechnology R&D. These data illustrate once again just how small and highly inter-connected the biotechnology intellectual and industrial research communities are in South Africa (see http://www.BioPAD.org.za for the names of the Board of Trustees).

BioPAD is organized along similar lines to Cape Biotech. It offers a one-stop suite of human resources, enterprises, licensing support activities for new biotechnology companies. BioPAD supports a website and was the first BRIC to allocate money for support the establishment of biotechnology companies. To date, BioPAD has allocated US$12.5 million (R135) to be spent over three years. According to the Bipod's CEO, Butana Mboniswa, the emphasis in awarding funds has emphasized animal health, industrial environmental, and agriculture forestry. BioPAD is making an effort to have a coordinated strategy of staggering projects in terms of when each project reaches fruition. BioPAD works with the eGoliBio incubator in Johannesburg to nature and prepare small, medium and micro enterprises (SMME)

for commercialization to date; BioPAD has funded three initiatives that are scheduled to come into existence within 18 months to two years. Other projects that come on line later are being evaluated now.

A unique feature of BioPAD is that the organization is also establishing portfolio investment funds. To date BioPAD had made four portfolio investments (Interview with Butana Mboniswa, CEO, BioPAD, June 26, 2003). One of the portfolio investments is called the Seed Capital Alliance Platform for Enterprises (BioSCAPE). BioSCAPE offers seed capital for small and medium sized enterprises. in the VC market. BioSCAPE is an alliance between BioPAD and investors to support biotechnology initiatives. The close links between BioPAD and CSIR are also evident in the mission statement of BioSCAPE which states that the fund "endeavors where possible to fund businesses that are incubated at eGoliBIO Life Sciences Incubator" (http://www.BioPAD.org.za).

A third investment project, Vaccines and Enhanced Therapeutics Platform for Animals (VETPLAN), is described on the BioPAD web site as an effort to support vaccine development and production in the region such key "BioPAD has also supported Bioresource Centers Platform (BioCEP) which seeks to support Bioresource centers (BRC), including "Regional breeding programs and seed collections, Insect collections, Fungi Collections, Gene Libraries, etc. at various institutes."

A final initiative funded by BioPAD is called, Microbial Technology Platform(MiTEP). MiTEP is designed to promote the exploitation of microorganisms and enzymes in the area of mining, environmental, animal feed and industrial technologies. Examples of research and commercialization groups in the region mentioned on the web site include: Rhodes University Biotechnology Group, University of the Free State Microbiology Group, CSIR Bio/Chemtek and Environmentek Groups, Mintek Biotechnology Group, BHP Billiton etc. Mintek, together with its joint-venture partner BacTech Environment Corporation." According to the web site:

> "The Mintek-BacTech partnership was awarded the contract for supplying bacterial oxidation technology to the Beaconsfield Mine Joint Venture in Tasmania, which came on-stream in 2000. A 100 t/d bacterial oxidation facility was commissioned at Laizhou Gold Metallurgy Plant, China, in August 2001. The CSIR Bio/Chemtek biotechnology group has equipped laboratories for biocatalysts, process research and development as well as structural biology. The organization has pilot facilities up to 2000 l and semi-commercial Imbiza multi-purpose facility."

The web site goes on to not that there are also "opportunities to convert hydrocarbons from petrochemical industries (e.g. SASOL), starch from bioconversion industries (e.g. African Products) or fruit waste for animal feeds, and to use microorganisms or enzymes in converting waste into essential compounds has been demonstrated by several research and commercial groups in the region."

The CEO of BioPAD, Butana Mbonisa, stressed during our meeting that there are between 20 and 25 different animal vaccines (all developed from dead viruses), several unique South African microorganism, and industrial technologies that have all been developed and customized for African markets. What BioPAD hoped to do is help build enough links between universities, private enterprises, and industries in South Africa so that South Africa's customer base throughout Africa and beyond is expanded. If successful, the expansion of the biotechnology section should be able to create a lot of new jobs for South Africans (Interview, June 26, 2003). The first phase of the effort seems to have been completed. In a May, 2003 open letter to stakeholders that was posted on the web site, BioPAD management announced that they had committed to finance 21 consortium-driven initiatives. In the future they will not call for proposals as they anticipate that they will be approached for possible funding and will post update regarding new funding on the web site and in newspapers.

2.5c PlantBio

There have been a series of delays in establishing the third region biotechnology center, PlantBio that will be located in the Kwazulu-Natal region. The delays are due to several reasons, including disagreements about the mission of the third BRIC. Some long-time participants in the planning process for the BRICS attribute the delays and reduced funds allocated to the third BRIC to opposition by influential persons within the Dept. of Science and Technology, and the Ministry of Environment and Water, and the ANC Party who are opposed to genetic modification techniques in agriculture (Interview, Prof. Jennifer Thomson, Dept. of Molecular and Cell Biology, University of Cape Town, July 10, 2003). The original plan called for PlantBio to be a national BRIC that would service the entire country in the area of commercial agriculture, forestry, and plants. However, the mission has now been scaled back to that of a regional BRIC organized along the lines of the other two BRICS. Prof. Mark Lang, Chair of Plant Pathology at the University of Natal-Pietermaritzburg and acting CEO of the PlantBio, reinforced the idea that the planning process for a scaled down BRIC was nearing completion. He noted in July 2003 that he was finishing the final self-assessment (Interview, July 1, 2003).

According to Prof. Laing, PlantBio was initially designed to be a national center to promote the use of plant biotechnology for greater food security. The Rockefeller Foundation has funded much of the research on genetically modified agriculture of basic food stables in Africa. Progress to date on developing drought resistance stables (i.e., cassava, millet, maize, and soybean) was promising to solve the problem of widespread starvation in Africa (see Thomson, 2002 for more details). Prof. Laing emphasized that PlantBio plans to continue to this research tradition and was making research on drought resistant plants a key priority.

From his perspective, the research supported by PlantBio will be a continuation of existing government programs. The Innovation Fund had already played a key role in helping to develop several products in the area of Plant Health products, including biological control agents (i.e., fungi, bacteria, and viruses). Since existing insecticides are costly and have long-lasting harmful effects, most actors in the commercial agricultural industry are very supportive of the PlantBio concept while also being sensitive to potential consumer backlashes to products produced with GMO technology. Several groups in South Africa, who are opposed to the introduction of GMOs into the South African food supply, oppose the concept of a national center that would be promoting GM foods. This controversy was one factor delaying the establishment of PlantBio.

The government reaction to criticisms may help to explain why the vision for PlantBio changed from a nationwide to a region BRIC, with a reduced amount of public funds for the new regional center. Several academic researchers, led by Prof. Jennifer Thomson, crashed President Mbeki birthday party to tell him directly how disappointed they were about the small about of money that was now being allocated to PlantBio. No new proposals have been made to increase the funding for the new regional BRIC. Instead, in a second generation of funding proposals, the only change requested by Treasury was an increased emphasis on the need for more tissue culture proposals (Interview, Prof. Laing, July 1, 2003).

While Prof. Laing remains mildly optimistic about the future, many plant researchers are now openly pessimistic about what PlantBio can accomplish. This pessimism stems both from the limited amount of funds that will be made available and because it now takes at least eight years to produce a biotechnology product from plant research. A conservative estimates was that it requires about two years of academic basic research, three years to field test, and two-to-three years of additional tests before commercial production can commence.

Several plant researchers interviewed for this study felt that the establishment of the national bioinformatics network should help move plant researchers in South Africa move from second-to-third generation research. Prof. Laing predicts that the national platform to promote agricultural biotechnology will be relocated to CSIR in Pretoria and that researchers will contribute genes to a gene bank being established at CSIR. Thus, at this point as if PlantBio will not become a platform for sophisticated research or a molecular microbe selector for African plant breeders. What other missions PlantBio will have in the future remains unclear. In the interim, most South African plant researchers will probably not attempt to get involved in the "big science" state-of-the-art biotechnology research but will instead, continue to work more like a cottage industry working with well-established genetic modifications techniques.

2.5d. EdenBio – A Proposed Fourth Biotech Hub

An informal initiative, funded by business interests located primarily around the city of George, is trying to establishing a fourth biotechnology regional hub along the Garden Route Corridor of the Eastern Cape Province. The area is called the 'Eden of the Cape' due to its natural beauty. The location is renowned for the combination of beautiful, unspoiled beaches and nature areas, good infrastructure and for many days the area in South Africa with the longest periods of sunshine. The area around George is the heartland of political support for the former Afrikaans National Party. The former Prime Minister, P.W. Botha lives outside George in Inverness. During his tenure in office, Botha supported building a modern, then state-of-the art Technikon at George that is an extension of the Port Elizabeth (PE) Technikon. The campus is still attractive and remarkably modern look. The Technikon has plenty of office spaces and the labs spaces have adequate facilities to conduct state-of the-art scientific research.

Like all the Technikons in South Africa, the Technikon at George also has a well-established network of collaborations with several foreign institutions and companies. A recently commissioned feasibility study of the area notes that the institutional relationships cultivated by the Technikon at George includes the Tel Aviv School of Medicine (Idea to Industry, 2002, p. 8). The feasibility study on developing a Southern Cape Biotechnology hub was conducted in 2002 by the consulting group, Idea to Industry. Prof. van Biljon, Campus Director of the Port Elizabeth (PE) Technikon at George and Chairman of the George Chamber of Commerce commissioned the report. The Idea to Industry Report (2002) concluded that while the various stakeholders' holders were not interacting enough to describe activity in the region as a natural cluster, there were several natural areas that could be developed. Promising areas for future R&D include homeopathic medicines, cosmetics based on indigenous plants, pharmaceutical discovery, and downstream processing.

Currently, the primary economic activities in the area are agriculture and tourism. The region is the only area where SA Breweries, South Africa's largest brewery grows crops. There is some light industry (i.e., extraction facilities for essential oil), and several of the more successful biotechnology startup companies in South Africa, including Shimoda and MeyerZall (see below). According to Torsten Henschel, a consultant who is working to promote relocation of biotechnology business to the area, there are at least 12 successful biotechnology companies in the region (Phone interviews, June, 2003).

QdotPharma, the most successful private company conducting medical tests with human subjects, is located in George. MeyerZall rents space on the George Campus of the Port Elizabeth Technikon. Students and researchers at the George Technikon have access to research animals and plants that may contain valuable compounds for the pharmaceutical and cosmetic related industries. According to the Idea to Industry Report, a British company is in the process of setting up a horticultural tunnel to test pesticides related to MeyerZall's Technologies, and MeyerZall is looking at ways to transfer genes across cell membranes to make trees more resistant to stress and disease (2002, p.8).

The report goes on to note that there are extensive collaborations between the PE Technikon at George and other South African Technikons and universities. The Technikon will soon offer a unique course in environmental engineering. Provocatively, the report also notes that there are negotiations underway between the Technikon and a major biotechnology company to establish an Institute for Biotechnology on the Saasveld campus. The report claims that the establishment of the center would "firmly place the Technikon and the region on the global biotechnology map" (2002, p.8).

2.6 Funding sources

2.6a. Public Sources

The scarcity of capital funding for high-risk biotechnology ventures remains one of the problem areas that the National Biotechnology Initiative was designed to address. As the Innovation Fund Program to fund basic research related to biotechnology program closes down, the BRIC funding will become one of the few sources of public funds available to help commercialize biotechnology. Most academics report few viable alternative sources for basic research support since the size of basic research grants from the National Research Council, which is analogous to the National Science Foundation, are very small. Some research areas, notably science research related to developing vaccines and medicines for HIV/AIDS and other infectious diseases, have been extremely successful in cultivating foreign sources of funding while many other sectors engaged in biotechnology have not been successful.

2.6b. Private Companies, Private Investors, and Portfolio Investment Funds

An important trend in South Africa and worldwide is that many of the new, small but successful private biotechnology companies are opting to remain private. If a company remains private it does not have to disclose major investors or details about financial records to the pubic. This trend is particularly noticeable in the area of new medical-related products. Private companies worldwide remain guarded about the details of their proprietary processes and products. In South Africa the secrecy is due in part to a fear that good ideas will be stolen before funding and commercialization can be found.

South Africa doesn't have a local pharmaceutical base. Until recently, most activities have been in the area of sales and marketing for major multinational. For many of these new companies and for investment funds interested in biotechnology companies, the primary goal is to develop unique biotechnology processes that can be sold to larger multinationals once Phase I and II Clinical trials are completed.

The major players involved in producing pharmaceutical products include a large number of multinational companies focused on producing drugs from traditional medicine, For example, Pfizer developed an anti- obesity drug from a plant used traditionally by the San people in Namibia to stop hunger. A Swedish company has developed a cancer drug from a South African plant. Most South African biotechnology companies who are attempting to exploit indigenous plant and animal products already have or are looking for funding and collaboration with large national or international companies.

However, some of the small-to-medium biotechnology companies in South Africa are not looking for partners and are choosing instead to remain private corporations that do not sell public shares or trade on the Johannesburg or other stock exchange. If this trend towards private corporations increases around the world, it will become increasingly more difficult to monitor who is doing what. Thus the formation of private companies, along with the extensive use of off shore shell corporations may be a topic of increased concern among those charged with monitoring dual use of biotechnology trends in the future.

Another financial instrument that gained popularity in South Africa over the past decade are closed-ended portfolio investment funds that sell shares in many, sometimes hundreds of new companies. One such fund dedicated to only investing in state-of the art biotechnology is a new closed-ended portfolio fund called the BioVenture Fund.

2.6c BioVenture Fund

Several investment funds invest selectively in biotechnology sectors in South Africa. BioVenture is South Africa's first biotechnology venture capital fund. It is a closed-ended fund that was formed and closed by the end of 2001. BioVenture invests in South African companies, which have proprietary technology in the biotechnology and life sciences area. The fund started making purchases in January 2002 and had invested about R30 million as of June 2003.[27] BioVenture is managed as a joint venture by two of the five investors, Gensec Bank and a Black Empowerment Fund called Real Africa Holdings. Genbel Securities, the Industrial Development Council (IDC), and the International Finance Council (IFC) are the other three investors. The IFC, a member of the World Bank Group, is the only international investor. The IDC has invested about R80 million and owns about 25% of the total funds. The Parent Company of Gensec, SANLAM, is the second largest insurance company in South Africa. SANLAM is the single largest investment group with about 25 % of the funds portfolio.

As a closed-ended fund, BioVenture seeks to invest in a diversified range of companies that can make a profit and be sold for a profit within a 3-5 year time frame. Agriculture is considered to be a high-risk investment. No South African biotech agricultural start-up company to date has made a profit. The fund does not yet know whether South African-owned biotechnology firms in agriculture will be sustainable companies. The fact that Europe is still the main agricultural export market and the current EU policy regarding GM agriculture products makes it difficult for start-up agriculture to make a profit in South Africa. Thus, such businesses are currently too high risk for the fund. (Phone interview with Heather Sherwin, BioVenture Fund Manager, Cape Town, June 17, 2003).[28]

Instead, BioVenture has made six investments across a variety of biotechnology sectors. The goal is to diversity across all promising sectors except agriculture. The six companies invested in to date are:

1) Pharmaceuticals (SHIMODA)
2) Water bio-remediation (AMANDLA)
3) Medical devices (DISAVASCULAR)
4) Bioinformatics (ELECTRIC GENETICS)
5) Bio manufacturing (SYNEXA)
6) A Joint Venture with the local CSIR unit Bio/Chemtex

The following discussion summarizes the rationale for investing in each of the firms from the viewpoint of BioVenture fund manager, Heather Sherwin. The fund invested in the privately owned pharmaceutical company, Shimoda, because they have a process that can be used in drug discovery that relies on modifying molecules to take a different form. Details of the delivery system are highly confidential as the company is still in the process of licensing and has not yet started clinical trials.

[27] Gavin Goldblatt's estimate provided during an interview on June 16, 2003.
[28] The information provided in this section is based primarily on a phone interview with Heather Sherwin, BioVenture Fund Manager, Cape Town, June 17, 2003).

The water bioremediation company (Amandla) was acquired a year ago. The company owns the right to a technological process that uses micro algae and bacteria in wastewater for waste management. The company is relying on the potential of the innovative process for site clean up. What is novel about this process is that it uses genetic resources, new enzymes that also have uses in such varied applications as drug discovery and pollution control.

The medical device company, Disavescular, manufactures cardiac stints for arteries. The company is not trying to compete with large multinationals, such as Johnson and Johnson, but rather is targeting markets in the developing world. The stints are cheaper to manufacture than existing ones and are based on an innovated design due to materials used to produce the stints. The company is counting on demand for their product because many of the large companies have stopped innovation. Sherwin claims the stints are highly regarded in New Zealand.

In the area of bioinformatics, BioVenture has invested in Electric Genetics, the first private bioinformatics company that grew out of research at University of Western Cape. Electric Genetics is presently the only bioinformatics commercial company in the country. The private company was created in order to market smaller, customized bioinformatics architectures for companies so they would no longer have to rely on large package solutions offered by existing companies.

In the biomanufacturing sector, BioVenture has invested in Synexa-Bio Life Sciences, who uses bacteria to manufacture antibiotics for pharmaceuticals. Their process is patented and allows for cheaper manufacturing. Additional details are confidential but the ultimate goal seems to be to sell the process and the genetically modified microorganism to a large multinational. [3]

The sixth BioVenture investment is a joint venture with the local CSIR Biotechnology division, Bio/chemtex. The new company called, Mbuyu, will manufacture fine chemicals using a standard process and technology package for environmental work. BioVenture and the CSIR each hold an equal number of shares in the total issued share capital of the company with both groups having two directors on the Mbuyu board. A non-executive, independent Chairperson, Joyce Matlala, from the Development Bank of South Africa has been appointed. A CEO for Mbuyu will be appointed before the end of the year. Mbuyu will pay the CSIR a share of any future royalties or revenues that may be earned as a result of the exploitation of the CSIR-developed technologies and these royalties or revenues will be negotiated on a deal by deal basis (see "Media Release," CSIR Homepage, July, 2002 and www.mbuyu.co.za for more details.)

2.7 Innovative Start-up companies

While much of the biotechnology R&D in South Africa today is about a decade behind techniques used in the developed world, a few, small start-up companies are developing novel technologies. Four companies whose current R&D activities are among the most sophisticated are described in this section. The first company, Synexa, uses a patented process to manufacture microbicides in a small, membrane bioreactor. Two other companies, Shimoda and MeyerZall, are both located close to each other in the George/Garden route area. Both companies are developing unique drug delivery processes and platforms. Many analysts in South Africa call Shimoda the most successful of a dozen or so new biotechnology startup companies that have been established in South Africa in recent years. Shimoda researchers are working on applying a unique drug delivery system to deliver drugs at the intracellular level.

MeyerZall is an established company that was founded by a man who developed a unique topical process called Emzaloid while searching for a method to deliver medicines for psoriasis sufferers.

MeyerZall is now using Emzaloid to develop a drug delivery system that can deliver the drug directly to cells as well.

The technology of a forth company, Biological Control Products (BCP), is not as sophisticated as the other three. The R&D activities of this new biotechnology start-up are described in detail because it is the only company in Africa currently producing biopesticides for clients in Africa, the Middle East, Europe, and the United States.

The intellectual property that forms the basis of the company's current commercial products for each of these companies is based on basic research insights developed within university, science (i.e., CSIR), or industrial lab in previous years. Synexa is using patented processes developed at Rhodes University. The original research/owner of Shimoda Corporation, Lawrence Pinkler, conducted his advanced stages of research at the laboratory facilities at Aspen Pharmaceuticals, one of South Africa's largest drug companies, MeyerZall is unique for developing it's patented process in a private lab.

Three of the companies, Synexa, MeyerZall, and Shimoda laboratory facilities are all using facilities at a South African Technikon campus. BCP's offices and lab facilities are located at a small industrial park several miles outside of Durban. All four companies are in the process of expanding and upgrading their current laboratory facilities. Three of the four companies are private companies with no plans to go public and sell stocks.

2.7a Synexa Life Sciences

Synexa Life Science is a small startup company consisting of five management and laboratory personnel, including the senior scientist/CEO, Dr. Winston Leukes. Synexa rents lab space at Cape Peninsula Technicon in Bellville, a commuter city adjacent to Cape Town. The primary revenue-generating products of the company today are fine chemicals used by researchers worldwide. Dr. Leukes describes the company's patented core technology as "second generation bioprocessing" that uses a fixed form bioreactor to get a small product to market" (Interview, July 10, 2003).

The initial focus on manufacturing small amounts of fine chemicals for research purposes was part of Synexa's business strategy of getting a revenue-generating product to market that would pay for additional R&D. Synexa produces fine chemicals, primarily enzymes, for Sigma Aldrich, a US distributor of fine chemicals used in scientific chemical reactions.[29] Synexa never sees the end users. Dr. Leukes and his associates noted that they were surprised to find out when they first started out that there are no export or import controls or other restrictions on the fine chemicals even though some of these chemicals are toxic antibiotics in high concentrations (e.g., growth factors).[30] Synexa researchers do have to register toxicity tests on products such as cyanide.

[29] Mr. Justin Devine, the Business Manager at Synexa, emphasized that Synexa had wanted to have a firm foundation of revenue and capabilities before they scaled up their production procedures. They believe that their small size and ability to shift product production is one of their current strengths, especially in the field of medical supplies where it was difficult for small players to earn descent yields (Interview, July 10, 2003).

[30] Synexa does not have to be accredited to produce these fine chemicals. Instead they register the small quantities they produce in South Africa. They also register toxicity tests on products such as cyanide. They noted that anyone can purchase fine chemicals, including fugal toxins on line from Signma Aldwich at www.signma-aldwich.com. As far as they know, Sigma Aldwich doesn't even do a credit check. Since the customers are researchers, there is an assumption that university ethnic committees would be the first-line of control against abuse of this source of chemicals.

Dr. Winston Leukes is a young academic who received an advanced degree in biotechnology and later headed a Biotech Masters of Science program at Rhodes University. Dr Winston recently left academia to try his hand as a biotechnology entrepreneur. The intellectual property (i.e., the cell culture technology) currently used by Synexa was developed at Rhodes University and Cape Town University during a period when academic researchers were considered the sole owner of intellectual property developed in university facilities. The lax intellectual property rights regulations at Rhodes University and the ability of Dr. Leukes to find a niche export market are the main factors that allowed them to establish a company. Starting about a decade ago, South African universities started to change their intellectual property policies. Today, the major research universities have policies and regulations in place that are similar to those found in developed countries. Dr. Leukes noted that one reason he decided to leave Rhodes when he did was to avoid having to share royalties or pay fees to the University of Rhodes under new regulations (Interview, July 10, 2003).

Synexa's R&D activities are focused on exploiting tissue cultures (see Table 5). The company is the only one in South Africa who has a patent on the tissue culture umbrella technology. The small bioreactor is currently used to grow mammalian cell cultures and develop pilot scale production of pharmaceutical products, including metabolites for cancer and AIDS research.[31] Although they only needed a pilot scale reactor to produce metabolites for use in cancer and AIDS research, Leukes and his associates are in the process of setting up a larger, more sophisticated laboratory so they can scale up their production procedures.

The company plans to expand its product line in several directions. Synexa was one of 15 companies who won a highly competitive position on the short-list of possible project in line to receive a start-up grant form CapeBio, the BRIC for the Cape region in July 2003. Their proposed project will use a unique patented cell culture technology, originally developed at the University of Cape Town, for the manufacture of high value but difficult to produce microbial secondary metabolites for the life science and pharmaceutical industries. Even before the project was announced, the company had gained attention for its methods of metabolizing new substances from fungi using a micro reactor. The protocol used for growing batches of the microorganism is unique.[32]

Synexa has also cultivated partnerships with several companies in South Africa and abroad. Synexa has a sublicense from Merck in San Diego to manufacture microorganisms for biomedical research. They also have a partnership with the Massachusetts-based company, Waters HPRC, for a water purification technology that can be customized. Synexa also has patents pending for a novel platform, including a solid-state fermentation platform. They are using this platform to explore such questions as which organisms are required for fermentation? Can the hardiest microorganisms be improved? And will improvements optimize yield? They are working with several polymers that will have embedded genetically modified microorganisms. Dr. Winston Leukes, president of Synexa, and his associates plan to undertake mutational studies to select the hardiest microorganism.

Synexa is also working with a new company, Franschhoek Waste Treatment Delta Spuralina, who was attempting to exploit algae for feed makers. The target customers for the new company were established South African companies, including the large chemical corporations such as Sasol, the Lysine Project S.A., and BioProducts. Since the company is involved in soil bio-molecular waste treatment, Dr. Leukes and his associates are exploring whether their procedures can be use for waste disposal. Synexa is

[31] The technology differs from the hard body bioreactors used by Procter and Gamble.

[32] Estimate offered by Gavin Goldblatt, Catalytic Investors, during phone interview, June 15, 2003. For more details contact the Business Manager at Synexa, Mr. Justin Devine (jdevince@synexa-bio.com) or www.syneza-bio.com.

also interested in developing procedures to use microbes' metabolites for prospecting and mining waste cleanup with the other company (Interview, July 10, 2003).

Another product under develop was a miniaturized system that promised to work better in small batteries. This and other product lines being developed by Synexa illustrate how the lines between biotechnology and chemistry applications become blurry. This fusion of biotechnology and chemical research is a common characteristic of the current generation of biotechnology start-up companies in South Africa who are all trying to find several different niche markets.

In the future, Synexa plans to expand the range of organisms that they produce. Dr. Leukes and his colleagues, like most research groups working in the Western Cape, are interested in building up a culture collection of rare organisms that includes the thousands of unique flora and plant species found only in the Cape. Dr. Leukes grew excited as he described how a 50-mile radius in the Cape remained unexplored. The potential products that interest him the most are potential cancer cures that may be developed using unique tree barks found only in the Cape. He also is excited about the large number of potential bioprospecting opportunities that exist for those willing to exploit indigenous remedies. He noted that the indigenous people of the Cape, the San or Bushmen, had recently demanded and received substantial royalties from Pfizer for an appetite suppressant that had been developed form the Bushmen's ancient remedies. Dr. Leukes shares the view of most Cape researchers that there are large numbers of opportunities to develop new products from Cape plants since every plant and fungi has microbicides that can be exploited.

Synexa also plans to explore the usefulness of microbes located well beyond the Cape, including water soil blasts found in Antarctica in the future. Winston Leukes is hoping to take advantage of the fact those South Africa claims hundreds of miles of in the South Atlantic and portions of Antarctica as national territory. Like many biotechnology researchers in the Western Cape, Dr. Leukes is interested in seeing more regulations that will protect beneficiaries of bioprospecting of the region's plants and flora in future years, including those at sea and in Antarctica.

Table 5: Synexa Technologies and Products

Products	**Application**
Microbial Metabolites	Research & Pharma
GM Microorganism	Water purification
Research & Mutational Studies (Selective pressure)	Soil Bio-molecular waste management waste clear-up
Small batteries technology	Commercial industry
Explore new & rare flora in Cape, SA	Bio-remedies from unique plants
Proposed exploration of Antarctica	Microorganism from hot water soil blasts

2.7 b Shimoda Biotech (Pty) Ltd.

Shimoda is developing a delivery system that enables drug molecules, proteins, and genes to be delivered to selected sites within the human body in an efficient and effective way. The CEO of Shimoda, Mr. Greg Gilbert, describes his patented drug delivery process as one based on

a synthetic protein that creates a vector by unenveloping and hallowing out the virus from the inside of the cell, as a unique process (Interview, July 2, 2003). Shimoda synthetic protein acts like a blue tongue virus. Once inside the cell, the immune system breaks up the virus, infects the cell, and presents it as an antigen on the surface of the membrane. The incorporation of the synthetic protein into the membrane of cancer cells will void the replication ability of cancerous cells.

Shimoda currently uses three platforms for drug delivery systems:

1) The novel viral drug delivery system described above that targeted intra-cellular delivery of drugs, proteins, and genes primarily for delivery of concern therapeutics;

2) Cyclodextrin-based drug delivery systems combined with existing drug molecules; and

3) A vesicle-based targeted delivery system utilizing modified cyclodextrin chemistry for the delivery of small molecule drugs.[33]

Today, Shimoda is listed on the Johannesburg Stock Exchange (JSE) and is backed by several large investors, including the financial services group Peregrine, Aspen, Bioventure, and several private investors who have provided additional venture capital funding to Shimoda. Shimoda uses laboratory facilities at the University of Stellenbosch and Cape Town University, and has some modest laboratory facilities in a building adjacent to Greg Gilbert's country home in Plattenburg.

Gilbert is in the process of building a 700 square meter molecular biology laboratory, estimated to cost about R200 million, behind existing laboratory facilities on his country estate. The estate is located down an ancient unpaved road in Plettenberg Bay, south of George along the Garden route. The total staff of the company is 23 and consists of 15 PhD's and 6 individuals with MS degrees. Shimoda researchers use proteonomics for research on hypertension, Alzheimer, TB, and HIV/AIDS. Genomic are used for the elucidation of genes for cancer and to try to discover novel gene in tumors. Mr. Gilbert said that Shimoda had recently made some interesting progress in their basic research program but he did not want to talk about it as none of the work had been patented yet.

Gilbert claims that his company is the only one in South Africa that is currently using nanotechnolgy to produce a capsivirus vector based on protein sequencing. He noted that many scientists have claimed that it is impossible to use this process for drug treatment. However, Gilbert notes that the synthetic protein approach is based on 10 years of solid science.

Gilbert believes that one of the advantages of his delivery system is that it can be used to administer anything from drugs for cancer therapy to delivery of drugs for crowd control. Greg

[33] Shimoda had developed two other compounds using cyclodextrin technologies by 2001. Cyclodextrin speed up the rate at which the body absorbs drugs by up to eight times. One of these compounds carries a commonly used anaesthetic and is currently undergoing first phase clinical trials, while the other carries an analgesic and has progressed to second trial stage.

Gilbert is interested primarily in using the technology to administer drug for epithelial cancer and for vaccine production.[34]

When asked about the suitability of the capsivirus approach for dual use purposes, Greg Gilbert noted said he doubted that the technology would be used by terrorist because it required sophisticated equipment and training to use. However, he noted that the platform might be an excellent one for assassinations. All one had to do was change the immunogenic agent to add a toxin or lethal agent ball and one had an extremely efficient way to target nerve cells with very small doses. The problem is that it wouldn't be cheap. He said it certainly wouldn't be his first choice if he were a terrorist or government looking for a new weapon or weapon of mass destruction because it would be too expensive. He also emphasized that someone would have to be able to cut the costs of manufacturing proteins and delivering specific nano balls.

In response to the question of whether the Shimoda patented capsivirus process could be used for diagnostic purposes, Shimoda's chief microbiologists, Dr. Marike Appel, said she thought the platform might also have some potential for diagnostic tasks (July 3, 2003).

The central unanswered question about Shimoda's capsivirus approach is whether the capsivirus approach can be scaled up? If it proves possible to use the approach in large-scale applications there may be a huge market for Shimoda's patented drug delivery approach.

Several market experts and microbiologists in South Africa who have reviewed Shimoda viral-based delivery system found that it was a unique approach. While market analysts worry about whether system can be scaled up for use with vaccines, Mr. Greg Gilbert insists that he isn't interested in developing a fully integrated systems approach found in many companies in the developed world that sell lead compounds to US and European pharmaceutical companies. Instead, Shimoda strategy is to develop and validate the proof of concept of the molecular models for specific ingredients using the Shimoda patented platform. Gilbert wants to sell the molecular models for specific drug delivery to major US pharmaceutical companies such at Bristol-Myers and Scribb (Interview, Greg Gilbert, July 2, 2003).

In 2001, Shimoda acquired certain cyclodextrin-based products and technologies from JSE-listed pharmaceutical company Aspen Pharmacare Holdings Limited, the second largest pharmaceutical company in South Africa. In exchange, Aspen became a shareholder in Shimoda.[35] Shimoda received another large influx of capital in 2001 when BioVenture, an 80 million rand biotechnology venture capital fund managed by Gensec Bank and Real Africa Holdings, bought an unspecified R12m minority stake in Shimoda. BioVenture Fund manager Heather Sherwin says the investment was motivated partly by Shimoda products and scientific and management skills, but also as it have already started to yield cash. "Shimoda has a substantial product pipeline, and some of its products have near-term cash generating abilities," she says. "This is unusual in a young biotechnology company as the drug development cycle tends to be so long." (Marrs, 2001).

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[34] Gilbert said he was also involved in another project funded by DARPA that involved developing an operating system language with World Wide Objects that was very intuitive. He didn't want to talk about this project since he said the United States government already knows all about it. He said he worked with Anne Robles at DARPA.

[35] Shimoda is using basic research in science that was developed in an industrial rather than academic laboratory environment. Shimoda uses research developed by Gilbert's former partner and druggist, Lawrence Pinkler. Before his recent death, Pinkler was in charge of innovative research at SA Druggists. Prior to this position, Pinkler worked at Aspen Pharmaceuticals, the largest drug manufacture in the hemisphere. Pinkler developed a stable oral diclophanate treatment for epithelial cancer while working at Aspen (Interview with Otto Mueller, Managing Director of QdotPharma, George, July 3, 2003). Pinkler and Greg Gilbert, an inorganic chemist by training who worked for several years in the uranium mining industry, started Shimoda in the mid-1990s to focus on the research and development of novel therapeutic compounds, with a focus on cancer therapeutics.

Shimoda used the IT acquired from Aspen to quickly generate revenue. In 2001, Shimoda sold the first license to a US pharmaceutical firm, Innovative Drug Delivery Systems, to use the cyclo- dextrin technologies to deliver the common anti-inflammatory drug, Voltaren, in a water-soluble compound derived from glucose in 2001. The water-soluble compound, to be marketed as Diclofenac, will undergo the final phase of the laborious clinical testing process in the US, and could be on the market by 2005. Gilbert claims that his company is the only one in South Africa that is currently using nanotechnolgy to produce a capsivirus vector based on protein sequencing.

Since the company sold its first license in 2001 the firm has used the revenue from the sale of the cyclodextrin products to fund further R&D on targeted drug delivery systems. Shimoda, like other biotechnology start-up companies in the medical field in South Africa, continues to seek international partners for collaborative research and to sell licenses for their products or processes to large corporations in South Africa or abroad. According to Greg Gilbert, Shimoda is currently collaborating in research with Jack Johnson at the University of Rhodes and with researchers at the University of California researchers at Davis and La Jolla (Scripps Institute). These California collaborations go back to the early 1990s and involve research to elucidate the crystal structure used to bind the drug to individual cells.

An anesthesiologist in Pittsburgh, PA, Lyn Phystler, is using his dicholfanate induction agent emulsion system. Gilbert claims that over $30 million dollars in revenue have already been generated from his method, which is licensed, to Johnson and Johnson for use in the United States, and to another company for sale outside the U.S. (i.e., Europe and Japan).

Shimoda also conducts research into the development of new cancer therapeutic and diagnostic compounds. The drug discovery effort seeks to combine a unique virus-like particle that was found in the local Titikalma Forest by Prof. Don Henry (Rhodes University) with a capsivector to deliver genetic material to cells. According to Dr. V. Wells, *"this technique holds a great deal of promise for gene therapy advances"* (personal communication, September 30, 2003). Shimoda is also using sophisticated computer-assisted drug design approaches for discovering new drugs based on the biodiversity of agents found in the Cape. The current research program includes fundamental research into the metabolic origins of cancer that aims to identify and improve diagnostics and treatments.

Greg Gilbert noted that he and his researchers discovered serendipitously that their nanotechnolgy could be used as a vaccine. [36] He negotiated a deal in 2002 to license the use of his delivery vector system in Austria. While the system is patented in Austria. Gilbert currently owns the intellectual property right to use in medical applications. Researchers at the University of Dublin in Ireland are using another one of his delivery systems. Gilbert noted that the recently established private company, BioVac, which has the exclusive contract to provide vaccines to the South African government, is interested in using the technology in vaccine production. In an interview a few days later, Dr. Katz, the Director of Research at Biovac, confirmed that the company was looking at Shimoda delivery system as a possible platform to delivery vaccines (Interview, July 8, 2003). The varied applications currently being developed by Shimoda are summarized in Table 6.

Table 6: Shimoda Technologies

Technology Examples	**Application**
Viral drug delivery system	Therapeutics
Cyclodextrin-based drug delivery system	Therapeutics, Diclofenac

[36] Other applications, such as agriculture applications, are outside the scope of Shimoda patent.

Vesicle-based modified cyclodextrin drug delivery system	Therapeutics
License protocols	Industry, Pharma

Shimoda and Synexa share several characteristics. First, they both are using the same approach to market some of their products. Synexa is licensing protocols while Shimoda is licensing a unique drug delivery system to large pharmaceutical companies. Both are succeeding financially after finding niche market opportunities. Both companies have kept their infrastructure costs down by renting bench space at public Technikons. In recent years, Shimoda has rented bench space at several locations, including the University of Cape Town, Stellenbosch, the University of Port Elizabeth, Rhodes University, and the Council and Science Research Organization (CSIRO) in Australia. While Greg Gilbert builds a new molecular laboratory behind his Plettenberg residence, Shimoda's Director of Research, Dr. Marike Appel, has used lab facilities at Stellenbosch University. She is currently in the process of relocating to laboratory spaces she has rented from Synexa at the Cape Technicon!

2.7c MeyerZall

Another South African firm, MeyerZall, claims to have developed a drug delivery system using a patented topical process called Emzaloid that can deliver drugs directly to cells. The delivery system was developed by a psoriasis sufferer and was originally designed for psoriasis, eczema, and other skin problems. However, the system is current in clinical trails as a method of drug delivery. Research is also proceeding on the feasibility of using the Emzaloid method to deliver vaccines (Interview with Kate Aspden, June 17, 2002; Interviews and presentation at MeyerZall on July 3, 2003). The major source of revenue for the company is from sales of a treatment for psoriasis called Lintar.

Recent R&D applications of the Emzaloid method as a new drug delivery system were developed from the initial product. MeyerZall also has several other products in the pipeline that they didn't want to talk about several of these products because they had already signed proprietary confidentiality agreements with other actors. One of these projects is designed to develop a new process for micro delivery to cells. MeyerZall researchers are working with researchers at the University of Cape Town on a collaborative vaccine research program to develop a DNA vaccine for HIV-AIDS. The company has another proprietary agreement with the new vaccine production company, BioVac, which is a spin-off from the former State Vaccine Institute. BioVac is interested in using the MayerZall process to produce rabies vaccines. MeyerZall senior officials also noted that a company called BioClone, located in Johannesburg, is interested in their process. They are also working on a new product with a United States-based company to control biofilms for water purification.

The offices of MeyerZall are located on the Saasveld Campus of the George Campus of the Port Elizabeth Technikon. The Technikon was built for the CSIR by the former apartheid President, PW Botha. The George/Garden Route area was his original political constituency and where "PW" lives in retirement today. Although the P.E. Technicon at George was built over two decades ago, they are in very good condition. MeyerZall occupies a large two-story building on the campus and is currently expanding its laboratory facilities.

MeyerZall is older than most biotechnology start-up companies having been established in 1988. The company is engaged in both proteonomics and genomic research but lacks access to large databases. They need a more powerful computer in order to be able to do three-dimensional studies of large molecules. Their current laboratory facilities are larger than most biotech companies or university BL-3

laboratories that I visited. Their research team is looking forward to having access to more databases and powerful bioinformatics computer programs once the national bioinformatics network is established.

According to a knowledgeable outsider, Otto Muller, the company is rated as one of the three top biotechnology companies in South Africa by many sources (Interview, July 3, 2003). The company earns most of their revenue from their topical diclophanate. Emzaloid as a topical cream is FDA approved and is used as by psoriasis suffers worldwide. Emzaloid consists of essential and plant fatty acids, nitrous oxide and a very large number of chemical and biological compounds. A small synthetic polymer is conjugated to the plant fatty acid. The key ingredient in Emzaloid is a fatty acid from a plant that is used for receptor targeting. Emzaloid has been found to enhance the effects of several drugs. Data from a bio-equivalence study of 60% of Emzaloid compared with 4 active combination drugs of choice used to treat TB were analyzed by Prof. Pete Smith of the University of Cape Town's WHO Collaborating Center for the Analysis of TB Drugs. The data supported the idea that an Emzaloid-based TB formula i.e. a four combination fixed-dose regimen, may be used effectively to enhance of the effects of drugs for multi-drug resistant TB (see Table 7).

Today, the company is developing one of the amino acids in Emzaloid in a water soluble form that can be taken orally and used as a delivery system or carrier for three, four and or perhaps more vaccines, including vaccines for resistant strains of TB, that are currently delivered through the blood stream. The Medical Control Council and all of the relevant ethical committees (i.e., SAMA, GCP, and GMP) have approved the new form of Emzaloid. The first clinical study will examine the side effects of the tuberculosis vaccine and will be conducted by Dr. H. McIlleron, Rheumatology Department at the University of Cape Town.[37] The company is also exploring the use of Emzaloid to carry antiviral compounds that may help HIV/AIDS victim better maintain their compromised immune system and to deliver malaria drugs.

Table 7: Meyer-Zall Technologies

Technology Examples	Application
Drug delivery (topical, emzaloid)	Therapeutics
Improved water based emzaloid	Therapeutics, TB & HIV vaccine

Emzaloid technology has the capacity to carry lipophilic, hydrophilic and insoluble compounds. The company's slide presentation noted that the ability of an Emzaloid to deliver an active compound to the nucleus of a cell indicates potential uses in fields such as oncology and gene therapy. While some classes of molecules are not ideally suited to emzaloid entrapment, the technology has the potential to be used as a weapon. When asked whether the technology could be used by terrorist, the Director of Research, Anne Grobler, said she felt the manufacturing process used to produce Emzaloid would be very easy to make and "could be make in one's kitchen." Since Emzaloid is close to a natural component in the human body, i.e. fatty acid and cell membrane, the active ingredients would be masked. No dog would be able to find it in a custom search (Interview, July 3, 2003).

2.7d Biological Control Products SA (Pty) Ltd

Biological Control Products (BCP) manufactures microorganisms for several purposes. BCP is one of the few South African companies with fungal biological control products registered for use in

[37] This collaborative research is currently conducting Phase II (non-human primates) trials at the University of Cape Town. The study is being directed by Drs. Carolyn Williamson and J Fanlee.

agriculture. According to the company web site, BCP is "ranked among world leaders in the development and manufacture of Biopesticides used to control pests in an environmentally balanced way." BCP has an exclusive manufacturing license and marketing rights for two innovative new Biopesticides, Green Muscle and Pl plus. These Biopesticides may be used on their own, or in combination with chemical pesticides. No special equipment is needed for either of products as both are easily applied using conventional systems. The United Nations Food and Agriculture Organization has approved Green Muscle for locust control in conservation and environmentally sensitive areas (www.biocontrol.co.za).

The company also conducts biomedical research using a sublicense obtained from Merck (San Diego) to produce drug agents for cancer and AIDS using novel platforms. The laboratory has a bioreactor that is used for pilot scale production of the drugs and several patents pending in the medical area.

The founder and CEO of Biological Control Products is Dr. Diane Neethling. Dr. Neethling is one of the few women who founded and directs a biotechnology company in South Africa. Much of the technology used by BCP is based on a unique, advanced manufacturing process, for producing fungal spore concentrate that was developed by researchers at CSIR. She was able to start her company with funding from a Trade and Industry Innovation Fund grant for the production of the principle income-generating product; a biological alternative to chemical control using natural fungi.

Like many other new biotechnology companies, Dr. Neethling plans to continue to run the company as a private entity and does not want to list it on the Johannesburg Exchange. Four investors financed her company. One of the first large investors was British Aero Space Systems, who invested 6 million Rand. In a second public stock auction, a large corporate investment, which she declined to name, invested 23 million Rand. The Industrial Development Corporation invested 4 million Rand and has observer status in the company. The forth investor is a private investor who she also declined to name.

The production process is being used to manufacture a variety of fungal spore products. These products are being produced at a new manufacturing plant located in KwaZulu-Natal between Durban and Pietermaritburg. Dr. Neethling is in the process of expanding the capacity of the new plant. BCP is one of the few facilities in existence anywhere that is able to produce Biopesticides in commercial quantities. Dr.Neethling estimates that there are about 25 companies in the world marketing Biopesticides. She explained that she needed to maintain modern plant facilities because she faced stiff competition from other companies based in South Africa, i.e., Bay Agro and several multinational companies, such as Nivantis and CABI Science, an Australian company (July 1, 2003).

BCP, like other Biopesticides companies, is attempting to market all over the world (i.e., in the U.S., Europe, and Asia). Her company also has customers throughout Africa and the Middle East. BCP currently sells to fewer than 10 agents, who in turn market BCP Biopesticides to customers in several countries. Her most important customers are located in Tanzania, Mozambique, Egypt, Ethiopia, and Saudi Arabia.

During a tour of the lab, Dr. Neethling jokingly referred to her production facility as possibly, "the largest bacillus shed in South Africa". There were hundreds of micro toxins, including several fungi, stored in plastic bags. Dr. Diane Neethling also noted that a complete list of micro toxins available in South Africa or any other country could be easily accessed at the North American pesticide database (PAN located on the web at www.pesticideinfo.org). For Dr. Neethling the three-plus years it takes to conduct efficacy trials was another serious issue for small companies such as BCP. (Interview, KwaZulu-Natal, July 1, 2003).

2.8 Types of Entities generating biotechnology R&D

2.8a University Research and Corporate Spin-offs

Most biotechnology R&D activities in South Africa occur in health and agricultural, industrial processing of wine, beer, or fine chemicals, and to a lesser extent in novel applications in mining and pollution control. The dominant pattern is for most initial discoveries to occur in one of the major research universities in South Africa: Rhodes University, Stellenbosch University, University of Cape Town, University of Pretoria, Witswaterand University, to a lesser extent the University of the North (formerly called University of the Orange Free State). Increasingly historically disadvantaged such as the University of Western Cape is also considered significant research institution in certain areas such as bioinformatics and genetics. Fewer significant new discoveries but many successful commercializations of basic research insights are accomplished by scientists working at one of the science councils (i.e., CSIR or ARC) or at industrial R&D at a corporate laboratory (see Appendix A for contact details).

Until recently, universities were not especially concerned about receiving a share of the profits from licenses or retaining control of intellectual property rights associated with biotechnology R&D. This situation started to change about a decade ago. By the late 1990s only the major research universities (i.e., Stellenbosch, Pretoria, UCT) had dedicated intellectual property technology transfers arrangements. Today most universities are developing such agreements in an effort to obtain a share of the profits from innovations developed in university laboratories. The shifting emphasis by the research universities is accompanied by efforts to facilitate the development of corporation spin-offs from university-based research.

SANBI and its spin-off company, Genetics Resources Pty. Ltd.

One of the more ambitious initiatives sponsored by the Innovation Fund is the South African National bioinformatics Initiative (SANBI). The central node of the South African National Bioinformatics Center (SANBC) is at the University of Western Cape (UWC). The initiative is trying to develop a nation-wide network capable of linking the major university and research centers together into a network that will facilitate collaboration by researchers at different locations and permit greater access to bioinformatics software and gene databases using satellite links to the UWC Center. Currently the only high speed Cray computer in the country is at the University of Western Cape.

The Bioinformatics Network recently asked for proposals to establish infrastructure at the majority of universities and will use peer review to decide which of the proposals will receive funding. The number of institutions involved in the effort is small as there isn't yet a critical mass of people needed to achieve the immediate objectives. Moreover, the initiative is still struggling to overcome a reluctance among departments to collaborate or share scare resources or the computer code necessary to develop a nation-wide architecture for soft targeting of drugs (Goldblatt, 2003). Few analysts expect much to come from the effort for several years. However, the first private company, Electric Genetics, was formed using software developed at SANBC. The immediate corporate strategy of Electric Genetics is to develop customized software programs for specific needs. The programs are designed to compete with available programs that offer one-size-fits-all packages. The customized program suites will be sold to interested corporate buyers in America or elsewhere (Interview with several industrial analysts).

The development of a national network around the South African National Bioinformatics Institute, SANBI, and the establishment of the African Center for Gene Technologies (ACGT) run jointly by the CSIR and the University of Pretoria are recent major steps towards building a nation-wide network capable of constructing the sophisticated computer architecture and genetic laboratory facilities needed for state-of-the art biotechnology research. The purpose of both SANBI and ACGT is to become regional and national centers of excellence in their respective fields, SANBI in bioinformatics and ACGT in gene and protein

discovery. Both institutions are also focusing on research related to health and agriculture (see Section 2.6c for more on ACGT).

SANBI aims to bring genome information, computational biology, and analytical tools to the entire South African research community. Since the national bioinformatics community today is tiny, a major focus in the future will be on building a larger scientific database in this area. Just how small the current bioinformatics community is in South Africa today was indicated by the fact that only 26 institutions returned a recent survey of bioinformatics institution. Only 23 out of the 26 institutions who responded to the survey indicated that they had submitted a BRIC proposal. The number of bioinformatics researchers at these 23 institutions across all levels (i.e. senior, mid-level junior post-doc) was expected to increase from 10 in 2002 to 37 during the period 2003-5. The number of post-doctoral students in bioinformatics went from 0 in 2002 to 12 today. The most frequently mentioned current and future bioinformatics requirements listed in the survey by the 23 institutions were: access to major DNA databases like EMBL/GenBank, BLAST, statistics, primer design, sequence restriction, phylogeny, training in the use of locally available tools such as BLAST/ALIGNMENT/PHYLOGENY/Sequence retrieval, access to scientific journals, software, and more computers.

The SANBI network is likely to become increasingly international as future multinational collaborations increase in South Africa. SANBI at UWC is already part of the S-Star consortium (which includes Stanford University, Sweden's Ursula University, National University of Singapore, and University of Sydney). The purpose of the S-Star consortium is to provide online bioinformatics courses to member institutions.

The first biotechnology spin-off private corporation formed from university-sponsored research in South Africa is Genetics Resources Pty. Ltd, a private corporation located at the University of Western Cape (UWC). Drs. Winston Hide and Rob Miller of Informatica Pharmaceuticals in the United Kingdom established Genetics Resources after developing a stack database. They now are willing to license use of the program for a fee. Dr. Hide and his graduate students have UWC since the mid-1990s have developed additional software programs relevant to state-of-the-art proteomics and genomic research.[38] Genetic Resources is the corporate entity set up and registered in the state of Delaware to sell the software. The primary activity of the company is to negotiate access fees to the stack database and to sell the rights to use several additional bioinformatics software programs developed by Dr. Winston Hide and his colleagues at UWC. Today, profits from Genetic Resources go to UWC, the company, and private investors.[39]

One of the most recent software program developed by Prof. Hide and his associates at UWC is eVOC, a controlled vocabulary for unifying gene expression data. eVOLK provides a vocabulary for looking at gene expression experiments for IDC9 (i.e., Clinical Diagnostic Codes) that is similar to the concepts created by scientific experts. The program links public available terms with genome sequence descriptions. According to the CEO, Tonia Hide, the program has received a great deal of attention by researchers around the world since it includes all the basic scientific techniques used in genetic research. Ms Hide noted that the program is of particular interest to large private environmental bio-industrial and agricultural researchers who need pinpoint accuracy of certain traits are transgenic research. The software

[38] Tonia Hyde, CEO of Genetic Resources describes the stack program as being similar to CAT clustering assembly but more rigorous. The business manager at Genetic Resources, Christina Ralmondo, noted that the program was like NCBI Unigene since both programs are used for the same purpose. STACK STACKPACK was developed in 1997. In 1998 the South African Dept. of Science and Technology funded SANBI to deep system functional software tools for research on phenotypes and genotype (Interview, Bellville, South Africa, July 9, 2003).

[39] Dr. Renfrew Christie, Director of Research at UWC, reports that Genetic Resources is producing an attractive amount of revenue for the university but declined to be more specific (Interview, July 8, 2003).

was used recently to design a micro array chip. It is also be used by health researchers as a more general analytical tool for data analysis. A patent for the eVOC is still pending (Interview, July 8, 2003).

Another computer program in the pipeline uses two tracks of data about two different organisms related by evolution. The program uses one particle line and transcript data about gene expression to compare the microorganisms. Ms. Hide described it as a novel approach to look for genes that have evolved some specific function. Current research is focusing on bacteria at 80 degrees Celsius and a gene of interest to the mining industry in South Africa. Dr. John Mickolana at the Harvard Medical School is working with Junaid Ganieldien, the chief bioinformaticist at SANBI, on the proof of concept for the project. An article examining the differences in strains of cancer, TB and several other viruses will appear soon in the journal, Genome Research. Dr. Valier Mizrali, along with colleagues at the University of Denver, are conducting similar horizontal gene research on tuberculosis-acquired genes this is similar to the type of research for which this program has been developed (see Section 1.3b and Boshoff, Reed, Barry, Mizrahi, et al, 2003).

Several aspects of Genetics Resources as South Africa's first university spin-off corporation may be useful for future comparisons with other university-generated biotechnology corporations in South Africa and other developing countries. To date most of the work using Genetic Resource software programs have focused on bacteria. Several of the programs proved useful for specific research tasks such as the validating processes related to TB research that take too long to validate in the laboratory. *The most recent proof of concept experiments currently being conducted with researchers at the Harvard Medical School are focusing on lethal or preventable viruses and are capturing data on the evolution of genes as they occur in nature.* All of the sales effort to date has occurred overseas in the United States, Asia, and Europe. However, several South African researchers plan to use the SANBI programs once SANBI comes on line.

Both Genetics Resources and the National Bioinformatics Network have used the model developed in the United States to structure arrangements regarding who will benefit from intellectual property rights related to biotechnology R&D. The National Bioinformatics network is now a separate trust with a corporate structure. Tonia Hide, as the CEO of Genetic Resources, along with other bioinformatics experts, will decide which projects to fund in the future. Royalties will be split three ways among the University, the researcher and Genetic Resources. The intellectual property rights developed through Genetic Resources will remain the intellectual property of Tonia Hide.

Ms. Hide and Ms. Ralmondo, the business manager, both stressed that agreements among researchers, the university and outside investors are still being established on the basis of verbal and follow-up email agreements. These informal exchanges illustrate the fact that there are no governance routines regulating academic technology transfers. Instead, regulatory oversight is conducted for specific agencies by regulatory agencies, such as the Medical Research Council, specific Acts of Parliament, and by university committees. (Interviews with Tonia Hide and Christina Ralmondo, July 9, 2002; Dr. Otto Muller, July 3, 2003, and Dr. Tony Mbewe, July 31, 2003).[40]

Thompson-UCT-Pannar Partnership

The current arrangement Prof. Jennifer Thomson has with another academic, a major seed company, and the University of Cape Town is similar to the three-way split used by Genetic Resources.

[40] For more information on policies regarding Intellectual Property (IP) status of research developed at South African Universities, contact Christo Veojoen at the U. of Cape Town (021 0342234), Rosemary Wolson at U. of Durban, and D. McCann at Witswaterand/Pretoria. Persons interested in more details should contact Tonia Hide, CEO Electronic Genetics Corp., or the business manager, Ralmondo Christina at UWC.

Prof. Thompson decided not to form a private corporation last year after Kofi Annan, the UN Secretary General, and several others persuaded her that she had to have very "clean hands" to remain an effective spokesperson for the advantages of GM foods. She decided she would be a less effective advocate for GM foods if she had a private company. Instead, she formed a partnership with a major South African seed company, Pannar, to produce transgenic varieties of seeds that are adjusted to African soil and climate. These transgenic seeds are patented and the royalties from the seed sales are split between Pannar, herself and another scientist, and the university.

2.8b CSIR, ACGT, and company spin-offs

One recent effort to promote greater commercialization of sophisticated biotechnology R&D at CSIR is the African Center for Gene Technology (ACGT). Dr. Jean Morris heads this office. The primary mission of ACGT is to develop industrial applications of biotechnology and implementing a new Technology for Developing Initiative to develop core skill and know how. As with all South Africa publicly supported institutions, poverty elimination is another major objective. The initiative to establish the ACGT was supported by funds from US AID, in addition to funds from the South African government. Persons interested in more details about the missions and activities of the new ACGT should contact Dr. Jean Morris (see Appendix B for contact information).

ACGT is a good example of the types of new public-university partnerships that the government is trying to encourage. Plans call for the African Center for Gene Technologies to be established within the School of Biological Sciences of the Faculty of Natural and Agricultural Sciences of the University of Pretoria. The new institution will be a joint responsibility of the School and CSIR Bio/Chemtex. The Director of ACGT reports to the Director of CSIR Bio/Chemtex and to the Dean of the Faculty of Natural and Agricultural Sciences. Although ACGT is an initiative started by the CSIR and the University of Pretoria, a longer-term goal of the organization is to involve more organizations and help create a world-class platform in gene technologies and genome analysis in Guetang Province. The ACGT plans to provide an integrating role for activities in genomic, proteonomics, structural biology and bioinformatics. Outputs will include students trained in the most modern technologies, top quality research publications, international patents with commercialization potential, and biotechnology start-up companies (Interview with Dr. Jane Morris, June 25, 2003; see http://www.acgt.co.za).

CSIR and University of Pretoria teamed up to do research in genomic revolution in an effort to discover and exploit unique Africa genes and to help establish the techniques and tools needed to exploit existing human resources. Currently techniques used in ACGT-supported projected include: DNA micoarrays to study genes and nature of African plants; searching for new drugs for malaria, particularly ones for TB and HIV; and malaria vaccine using a molecular modeling approach to model specific enzymes that focuses on the total genomic effect of drug rather than the organ. ACGT affiliated researchers are also working on protenomics applications including characterizing GM plants and the differences between modified and non-modified plants. Researchers also plan to study the unintended consequences of GM. If the European Union-CSIR 6th framework, currently being negotiated progresses permits it, ACGT researchers hope to do collaborative research in the future on food safety. Several ACGT researchers are interested in fungal contamination and metabolism of plants.

Specific ACGT project areas include: research on the enzymes in the saliva glands of ticks. Several outputs from this line of research are already patented by Hank Huismas of the University of Pretoria. Prof. Huisman is also working on novel vaccine delivery systems to counter African horse sickness by modifying stomach peptide to develop notorious difficult vaccines. The virus has a segmented double stranded RNA genome. Each of the ten-genome segments is a gene that encodes one of the ten virus-specified proteins.

Prof. Huismas's research is designed to determine the role that the different proteins play in the structure and replication of the virus. Specifically, his group is trying to identify the major immunological determinants of the protein on the surface of the virus particle (see http://www.acgt.co.za/Prof.Henk.Asp for more details).

Another project focuses on the genetic architecture of Eucalyptus tree species in terms of fitness, growth and wood properties. The project involves a combination of molecular genetic approaches such as AFLP mapping, candidate gene mapping and quantitative trait locus (QTL) analysis in inter-specific pedigrees of Eucalyptus species. The project focuses on two commercially important Eucalypt species, E. grandis and E. globulus.

While no fourth generation research is currently being conducted at the Bio/Chemtex or FoodTeck Divisions of CSIR or at the University of Pretoria, one of the missions of the ACGT, along with researchers at the University of Pretoria is to supply the necessary human infrastructure to develop sophisticated state-of-the art bioinformatics tools and research programs. ACGT was established in part to promote sophisticated research and Dr. Morris plans to participate in the Bioinformatics network. The goal is to conduct a coordinated approach gene expressions on every gene and organism to be able to link genomic at the molecular level.

The necessary physical infrastructure, a 500 square meter Bioinformatics Center, is nearly completed. A new building at the University of Pretoria will soon house the Bioinformatics Center and the Bioinformatics faculty at the University of Pretoria. When the Bioinformatics facility is completed, the ACGT facility and SANBI will comprise the two largest node facilities within an emerging National Bioinformatics Network. Details about the equipment that the new facility will contain are available at the web site, from Anton Barnard (Computer Science) and Furie Joeberg, or from personnel affiliated with the CSIR IT division. The primary users are projected to be researchers working on medical applications. Several plant and forestry researchers affiliated with FBBI (see 2.7) also plan to use the new Bioinformatics Center extensively.

CSIR Bio/Chemtek Division and Mbuyu Biotech

In August 2003 the Bio/Chemtek Division of CSIR made two important announcements related to biotechnology R&D. The first was a call for participations at the first annual Bio/Chemtek Conference sponsored by CSIR. The preliminary program and poster tiles for the conference to be held in August are listed in Exhibit 4. The program is one indicator of current research questions, policy issues and concerns, and some of the key actors who are involved in either industrial and commercial agriculture biotechnology R&D in the greater Guetang area. Exhibit 2 is also useful for illustrating the close working relationship between CSIR in Pretoria and the University of Pretoria.

An important goal of ACGT is to provide opportunities to empower African scientists from historically disadvantaged backgrounds, to enable them to play a leading role in the biotechnology "revolution" and to build links among researchers at the University of Pretoria, CSIR and ACGT. (A list of researchers affiliated with ACGT and their individual interest is available at http://www.acgt.co.za/ People.asp for individual profile and research interest). Information about ACGT's Intellectual Property Portfolio, which include an antiretroviral treatment, HIV inhibitor, metabolic inhibitors, or detection of Stenocarpella (Diplodia maydis) can be obtained from Terry Watson, of the Intellectual Property Portfolio (see twatson@csir.co.za).

The Bio/Chemtek Division of CSIR also announced in August the formation of a new South African Company, Mbuyu Biotech. The new company is a joint venture between Bio/Chemtek and and the BioVenture Fund, the specialist biotechnology venture capital fund described in 2.4a. Mbuyu has been

granted a worldwide license to further develop, demonstrate and commercialize three CSIR-developed biotechnology-manufacturing processes that are being spun out from the CSIR for further technology packaging. Mbuyu and CSIR are continuing to negotiate the exploitation of several additional CSIR biotech-processing technologies. According to the above cited media release, "Mbuyu will also seek to expand its biotechnology portfolio with promising new biotechnologies developed at local incubators, universities, and other research organizations."

Biosys

Another example of a relative new biotechnology company with roots in CSIR Bio/Chemtek research and development is BIOSYS **(**http://www.csir.co.za). In a recent press blurb, BIOSYS announced that it had exported half-ton of oil from South African organically grown geraniums to a leading International Cosmetics Corporation. This is considered a landmark for South Africa's budding essential oils and bio-extract industry.

Future CSIR R&D trends

CSIR Bio/Chemtek plans to continue their long-standing pattern of spinning off new biotechnology companies and working with new research partners or investors. CSIR has a good track record of finding solutions to specific applications but must contend with the same general problem facing all biotechnology R&D activities in South Africa today; how to find a place to market these applications. CSIR is currently at fairly early stages of pursuing biodiversity possibilities and Bio/Chemtek plans to continue working in areas of fermentation, biocatalysts, and any processes or procedures that can contribute to job creation. CSIR is a major employer for recent graduates with an advanced degree in scientific or management fields related to biotechnology. If CSIR is successful in the future in stimulating the formation of several new biotechnology corporation, it will make a meaningful contribution to the national goal of increasing the number of well-paying jobs for recent graduates in biotechnology. If it fails to promote a growing private biotechnology sector or is forced to cut back on current R&D activities, there will be an even larger glut of recently trained but unemployed post-grads in South Africa in the future.

The main focus of Bio/Chemtek's in the past was R&D related to agricultural fuel. While this area is still a major focus of R&D for the Division, Bio/Chemtek plans to continue diversifying its biotechnology activities. In addition to continued research on fermentation which occurs an amino acid factory in Durban, CSIR researchers are working on micro active microbe agricultural flavor fingerprint, how to use microbes to add nutrients to food, and on the ratio of nutrients in drying process to make either a liquid or powder. According to their web site, their most sophisticated research is a process to make fermentation biocatalysts. The Division also supports R&D on agricultural fragrance flavoring.

Bio/Chemtek works with Dr. Don Cowan, University of Western Cape, who has a library of floral environments, i.e. Fynbos DNA, and with Prof. van Zyl at the University of Stellenbosch on yeast. Generally, plant biotechnology, including culturing, manipulating, profiling and assaying genes is a small percentage of total Division's effort. Only 18 people are working on plant biology compared to 20 working on Fermentation, 20 in Biocatalyst, and 20 in Industrial Biology.

Instead, the main focus in plant biotech is on using African crops, i.e., GM maize and soybeans, to enhance the nutritional value of subsistence crops and genetic engineered pest resistance. South African researchers are already far along in both of these areas. The main problem however, is that South Africa has large exports of agriculture products to Europe and there is lots of uncertainty about the future given the EU's ban on GM imports.

In the areas of manufacturing and industrial processes, the Division is exploring the usefulness of using biological microbes isolated in soil for biological pest control and have come up with a specific application formulation that is now being marketed by a company called, Bicrobial Solutions. CSIR has a large program that is looking at pollution control and new approaches to waste treatment that is relevant to industrial water purification applications. For example, recent pilot studies of microbes at microbial fish frames suggests that microbes will be a more efficient way to remove waste in ornamental fish environments (CSIR web site and interview with Dr. Dusty Gardner, June 25, 2003).

Three points about the future direction of the BioChemtek Division at CSIR are worth noting. First, commercialization of biotechnology in the area of industrial and environmental processes will not be a major focus of future research. Dr. Rusty Gardner, Managing Director at BioChemtek explained that the profit margins are not high enough to make this a major area of concentration for CSIR (Interview, June 25, 2003). Second, although CSIR does have BL-2 lab facilities, CSIR researchers do not plan to work with hazardous organisms in the future. Dr. Dusty Gardner, explained that Bio/Chemtex had conducted a risk assessment and decided there wasn't enough demand to pay for cost.[41] This policy decision and the fact that CSIR is prevented with working directly with people in their charter are the most important reasons why Dusty Gardner does not believe dual use products can be generated from CSIR processes or procedures in the future. Third, while five-to-ten CSIR employees will be working on animal health with colleagues at Onderstepoort, Dr. Gardner does not see how there could be "covert research conducted under the cover of animal vaccine development because there not that much vaccine would be developed for medical application" None of the 80 or so CSIR employees who currently have the skills necessary to do generic protein based research are screened (i.e., background security checks) because there's no perceptions of need. Echoing statements he made in answering other questions, Dr. Dusty Gardner noted, "Biodefense is just not an issue." (Interview, June 25, 2003).

This report focused on the Bio/Chemtek Division of CSIR in Pretoria because it is the business unit at CSIR that provides technology solutions in the food, chemical and biological technology domains. However, there are eight other divisions at CSIR. Several other Divisions, i.e., DefenseTek, Environmentek, Kentex, Building, Transport, Miningtek, Material and Manufacturingtex, and Prochemtex, at CSIR units in Pretoria and around the country that are conducting biotechnology research that may be relevant to potential dual use. For example, CSIR is an important player in developing technology for fermentation line management. A small Structural Biological Group at CSIR, led by Colin Kenyan at Muldenfontain, has acquired the drug library from a large corporate that recent closed down their biotechnology division. The Structural Biological Group at CSIR is trying to locate novel proteins to use as enzyme targets.

Prochem is using chemistry and bioinformatics to identify a unique target reaction medium for Charrinase enzymes. This work is being conducted in conjunction with Structural Biology researchers at the University of York (UK). The Structural Biology unit at CSIR has many partners at colleges and universities in both Europe and the United States, in addition to commercial links with major commercial multinationals such as Pfizer, Cargil, Glaxco, and Nervatis.

CSIR also has a small group of researchers who are working on 8-10 hybrid protein expressions. The CSIR researchers are using genetically modified microbes for protein production systems, drug delivery, and for diagnosis surface displays of enzymes. CSIR has no gene libraries but is using aqua filter

[41] Recent annual reports for Bio/Chemtek supports Dusty Gardner's assertion by noting that CSIR researchers had produced their first growth stimulants in two years while dropping work on disease bacteria cultures. According to recent annual reports, no biotech product that can be marketed as alternatives to pesticides has been produced yet.

microbes from the deepest goldmines (3 kilometers below) available at the University of Free State. This collaborative process plans to produce a diagnostic kit relevant for identifying when glucose becomes gluconate. The product is viewed as an alternative to using a purifying process. While a comprehensive survey of all CSIR unites was beyond the scope of this report, contact information for key individuals involved in biotechnology research for each sub-sector can be found on the CSIR web page. Several CSIR contact persons are also listed in Appendix A.

2.8C Agricultural Research Center privatization efforts

The Agricultural Research Center (ARC) remains the principal agricultural research institute in South Africa for both the National and Provincial Departments of Agriculture. ARC was originally part of the Dept of Agriculture. ARC became Science Council in the SA National System of Innovation in 1990s. Since 1994 several of the research institutes have been consolidated. There are now 13, down from 16, ARC institutes. ARC has always sponsored research and development designed to promote agriculture, food and animal health. ARC researches institutes continue to be re-organized and are being encouraged to privatize ongoing R&D activities. While the major priority of ARC remains rural development, ARC institutes today are also expected to promote other national imperatives including: job creation, regional integration, urban renewal, human resource development, AIDS/HIV and crime prevention.

According to the ARC web page (http://www.arc.agric.za), ARC institutes activities since 1999 have contributed to the agricultural industry by releasing 32 newly developed cultivars / breeds, developing 13 technologies to control alien plant species, 3 new technologies to control animal disease and by training 9,000 in agricultural production and value-adding technologies. ARC is also involved in collaborations with several other countries and non-governmental organizations and plays a key role in transferring technology to farmers in South Africa, SADC, and throughout the continent.

Section I discussed the fact that several ARC institutes affiliated with Onderstepoort, the country's premier animal health R&D institute, have the capabilities to engage in dual use R&D. Relevant units include research groups working on: applied biotechnology, bacteriology, biochemistry, exotic disease Division, pathology, parasitology, rabies, virology, and a molecular biology lab unit. Section I also discussed recent concerns about the major spin-off company from Onderstepoort, OBP, the private corporation established in 2000 to take over biological production after this activity was privatized. Since several knowledgeable experts reported that the company had no current products, it will not be discussed here as a viable civilian biotechnology spin-off.

Today, the emphasis at ARC institutions is on privatization rather than innovative research in agriculture and veterinarian science. The 13 ARC and numerous other semi-private or private corporations created from ARC institutes are located throughout the country. Each institute is supposed to specialize in research relevant to the proximate region.[42] Currently, ARC employs about 4,000 individuals. Increased numbers of former ARC employees have been shifted to semi-private entities since the early 1990s. For example, less than half of the budget of Infruitec-Nietvoorbij, a key ARC food research unit in

[42] Most of the 13 current ARC institutes are located in Guetang. These institutes specialize in: 1) Dairy Science, 2) Plant Improvement Institute 3) Citrus Tropical Plants 4) Roodeplaat Vegetable and ornamental fruits, 5) the Soil and Climate Institute, 6) the Small Grain Institute in Free State, 7) Institute for Industrial Crops, 8) an ARC institute in Rustenberg, north-west of Johannesburg, 9) the Proteins and Organic Institute 10) Soil Climate and Water, 11) Onderstepoort Veterinarian Institute 12) Animal Improvement and Protections and 13) Infruitec Wine and Designer Crops in Stellenbosch and Grain Corporation Institute in Potschefstroom.

Stellenbosch now comes from public sources today (Interview, du Plessis, July 9, 2003). While ARC research institutes still engage in basic research, they are all facing increased pressures to commercialize and privatize their research in order to help reduce government costs and create more jobs. The shifting emphasis means the dual use research related to agricultural and animal dual research in the future is as likely to be occurring at private or public-private entities as at the long-established ARC institute such as Onderstepoort.

Onderstepoort is the only government animal research institute that was authorized to do biological research in past legislation. The major private corporation spin-off from Onderstepoort, Biocon, was covered in Section I. Two other ARC-affiliated institutions, the Foot and Mouth Institute adjacent to Ones port's campus north of Pretoria and the ARC Animal Improvement Center at Irene also conducts animal bacterial R&D using BL3 containment laboratory facilities. As noted in Section I, the Foot and Mouth Institute is now run as a private entity. It was originally established to investigate breeding practices for farmers, along with its core focus on animal disease. Today, it is engaged in several lines of sophisticated research, including using artificial intelligence computer programs for cloning research (Interviews with Dr. Wolf Katz, Research and Development, Biovac Institute, Cape Town, South Africa, July 8, 2003). [43]

The Biotechnology Division of the ARC's Vegetable and Ornamental Plant Institute, located at Roodeplaat, near Pretoria, is preparing to take over the long-empty laboratory faculties and offices of the former Project Coast front company, Roodeplaat Research Laboratories (RRL) (Interview Hack Jager, July 2, 2002). [44] The focus of the research group of the Biotechnology Division according to the web site is to "actively promote collaboration with other ARC institutes, the Council for Scientific and Industrial Research (CSIR), universities, agricultural industries and the National Department of Agriculture." Five focus groups share research programs within the Biotechnology Division and study such factors as abiotic stress, drought and heat that limit agricultural productivity. The aim of the program is to improve agricultural crops through identification and evaluation of traits associated with drought and heat tolerance in higher plants. Experience on drought screening includes crops such as potato, soybean, Vigna, Amaranthus, maize, Eucalyptus, Cajuns and sweet potato. Recent significant achievements of the Institute include improving indigenous ornamental plants, indigenous vegetable crops and natural products and hosting a UNESCO-supported education and training center (BETCEN) at the institute where a large number of scientist from Africa have been trained (For more details see, http://www.arc-aii.agric.za/v-arcroot/institutes/roodeplaat/roodeplaatmain.htm and http://www.ejb.org/content/vol1/issue3/abstract/6/index.html).

Several ARC research institutes are working on incorporating genes associated with drought resistance into potatoes, soybeans and other stable crops on an experimental basis using transformation techniques. The primary focus of research on crops has been on increasing disease resistance. ARC-Roodeplaat is playing a lead role in transgenic research. The first field trial of transformed potato (for PLRV resistance) in South Africa was conducted at ARC-Roodeplaat in 1997, under approval of SAGENE, the regulatory body for GMOs. Plant resistance to fungi is also being studied by determining the role of Polygalacturonase inhibiting protein (PGIP) (http://www.ejb.org/). A PGIP gene has been transferred to maize for control of Stenocarpella in cooperation with CSIR Foodtek.

Gene transfer technology is also being developed for cassava and sweet potato. The latter two crops are being given high priority because they both are an important resource for poor farmers. The ARC web

[43] A POC for the Foot and Mouth Institute is Dr. Pam Hunter. See Appendix A for contact information.

[44] It should be noted that there is no public indication that ARC's Roodeplaat Vegetable and Ornamental Fruits Institute of Ornamental at Roodeplaat was ever involved in past secret biowarfare research.

site also notes that the African horse-sickness virus (AHSV) protective antigen gene has been transferred to tobacco in order to produce large quantities of this subunit vaccine in plants.

Tissue cultures have been an important aspect of the Biotechnology Division of ARC-Roodeplaat for the last two decades. Tissue culture protocols for many ornamental and vegetable crops, including root and tuber crops such as cassava, sweet potato, and the wild potato (Plectranthus esculentus). Tissue culture of the latter is providing planting material to a community in the Northern Province of South Africa to help poor farmers re-establish the wild potato in the area. Protocols have also been developed for rapid multiplication of rare and endangered succulents and medicinal plants, and several species of Haworthia have been propagated in this way for re-establishment in conservation areas. Virus elimination techniques have been developed for potato, sweet potato and cassava to provide meristem-derived disease free material for use in propagation, breeding, in various gene banks, and to provide certified virus-free planting material to farmers and the commercial sector.

The breeding programs sponsored at ARC-Roodeplaat breeding are also using a plant molecular marker laboratory to provide a variety of services to clients including seed lot purity testing, trueness-to-type confirmation, cultivar identification and confirmation of parentage (See http://www.arc-aii.agric.za for more details).[45]

The Fynbos Unit of the Institute, located in the Western Cape at Elsenburg, Stellenbosch, plays a lead role in the commercialization of proteas and other Fynbos species through its research on breeding, propagation, plant protection and promoting of Fynbos as a viable commodity. Fynbos research is centered on the gene bank, which is a unique collection of living plants, identified for their economic horticultural traits and representing biodiversity in the species.

2.9 Biotech Professional Associations

Two of the best-known professional associations in South Africa are the Biological Food Fine Chemicals and Fiber Association headed John Southern, the biotech industrial representative on the Non-Proliferation Council. As noted earlier the association has not met for the past couple of years because most of the larger industrial corporate members are no longer actively involved in biotech.

The mission of a new biotech association, AfricaBio, headed by Josalyn Webster, is to promote acceptance of biotechnology and to publicize the existence of a new generation of very small start-up corporations. AfricaBio has several on going programs including activities designed to promote General Public Awareness and Training in Biotechnology, Regional Communicators Training Workshop, a Knowledge Center Project, Industry Training, Regional Public Awareness and Dialogue Project, and Curriculum Development for School. AfricaBio is also working with the CSIR and the Innovation Hub to establish a Bioincubator at Modderfontein (Guetang) that is designed to stimulate the development of small and micro-sized biotechnology businesses. AfricaBio also annually presents an award to a young scientist and journalists who showed the greatest commitment to distributing accurate information on biotechnology to the public. The organization worked with the University of Pretoria to develop modules on food and agriculture for use in secondary schools. These modules and more details on the above and other projects are available on the AfricaBio website (www.africabio.com).

[45] According to the web site the main techniques employed are RAPDs and SSRs. Marker technology services being offered use PCR. Marker technology is also being used for estimation of variation in Protea populations as well as germplasm management of sweet potato.

In mid-July, 2003 AfricaBio together with another organization, FANRPAN, organised a two days South African Development Community (SADC) Biotechnology, Policy and Trade workshop. The forum was designed to provide information for biotechnology stakeholders and decision makers throughout the SADC region on issues related to biotechnology policy and trade. A central focus of the meeting was how SADC countries could prepare for dialogue with the World Trade Organization. Delegates form 14 SADC countries, along with presenters from Europe, the US, Argentina and several African countries were among the 106 participants. A final report from the workshop and list of participants is also available on the AfricaBio website.

2.10 Training and Education

The most important centers for advance degrees in biotechnology related fields remain the five tier one research universities in South Africa, i.e., Rhodes University, Stellenbosch, University of Cape Town (UCT), University of Pretoria, and Witswaterand University. In the realm of plant research, the University of Durban-Pietermaritburg ranks in this group. Some biotechnology research and fairly large graduate education programs are also offered at the University of Free State, former Orange Free State, and other universities. A major change from the apartheid era is the prominent role that the University of Western Cape (UWC) plays today as the center for the new national bioinformatics network and the only site with a Cray super-computer. UWC is a historically coloured university that had a reputation as a second-rate institution during apartheid. It current central role in the national bioinformatics imitative reflects the commitment of the current government and many academicians to upgrade historically disadvantaged universities. The Director of Research at UWC, Winfree Christie, reports that he has had great success attracting world-class researchers, such as the head of the Bioinformatics Center -Winston Hide, back to South Africa (Interview, July 8, 2003).[46] The Technikon are also playing an increasingly important role as biological and biotechnology training centers and locations where small corporate research efforts is occurring.

Several novel vaccine research programs sponsored by the diverse departments and programs as medical schools, departments of virology, and plant microbiology reflect the unique emphasis in South Africa. The importance of finding vaccines and drugs to manage HIV/AIDS and other infectious diseases is a driving force in applications of biotechnology in South Africa. R&D in these areas is also fueled by huge amounts of outside resources that have become available for research on HIV/AIDS and other infectious diseases in the past five years. The Bill and Melinda Gates Foundation now figure as one of the most important sources for research funds, along with the more established European and American foundations and public aid programs. The emphasis on using plants rather than animals as the medium for new vaccines based on genetic modification techniques reflects a widespread interest to take advantage of the biodiversity of the country.

Despite the recent influx of funds for research on infectious diseases, an outsider is struck by the limitations and small scale of laboratory facilities being used at the major research universities. According to several researchers, UWC and University of Witswaterand are the only two universities with the facilities for sophisticated molecular modeling. Medical researchers at Witswaterand only obtained the first DNA microarrays at the university this summer. However, it is also important to recognize that the small scale and limited capacity of research facilities, and thus, the quality of instruction for graduate education is

[46] An ironic twist of political power, Winfree Christie, enjoys unusual easy access to senior members of the current government because of his long-standing support for the ANC. Christie spent nearly a decade in jail during the apartheid era for giving stolen classified documents related to the nuclear program to the ANC.

changing rapidly. This trend has significance well beyond the country since South Africa ill remain a key hub for scientific graduate education for Africans and many foreign students from developing countries for several decades.

2.10a Rhodes University

Prof. Winston Kirby started the first program M.S. program in biotechnology at Rhodes University in Grahamstown in 1987. Initially the program only offered courses in biotechnology relevant for commercial applications in environmental waste. Gradually faculty from several departments became involved in teaching courses and the program became accredited as a PhD program in the early 1990s. Several science departments merged during the 1990s to become the Department Biochemistry, Microbiology and Biochemistry. Currently, the program offers honors courses for undergraduates, has 15 students enrolled in the M.A. program (which includes two courses with Environmental Science, and has 30 PhD students enrolled in a Bioinformatics program that takes between three and six years. Most graduate students go on to do post-doctoral degrees and obtain jobs in industry. Most recent graduates are employed in industry with many finding jobs in recent years at different divisions of CSIR such as Bio/Chemtek or Food Technology. Key academic researchers associated with the program include Greg Blatch, who works on chaperons protein and Graham Bradly, formerly with the Biochemistry Department, who conducts third generation proteomics work. Dr. Rosemary Darlington is well-known for her work on enzymes cloning into bacteria [47] (Interview Dr. Winston Leukes, Synexa Life Sciences, Bellville, South Africa, July 10, 2003 and Rhodes web site insert).

2.10b Genetic Modified Agricultural Research, Department of Molecular and Cell Biology, University of Cape

Throughout this report references have been made to sophisticated medical research that is current being conducted at the University of Witswaterand, Stellenbosch, and University of Cape Town by researchers in the medical school. Much less attention has been given to research on genetic modification that is occurring outside of ARC laboratory faculties. One of the best-known names in GM agriculture in South Africa is Professor Jennifer A. Thomson. Her field research and efforts to popularize the research supporting use of GM in agriculture are well known around the world (see Thomson, 2002). Below is a brief description of the recent research projects conducted in her lab. These summaries are designed to illustrate the type of knowledge a coterie of students from around the world is receiving today at UCT.

According to Thomson, one of the big GM food successes among small-scale farmers in South Africa is Bt Cotton. A group of small-scale farmers living in the Makhathini Flats in Northern Kwazulu-Natal, in an area bordering Mozambique, in 1997 participated in a government approved field test of the relative effectiveness of Bt Cotton. Although it took several years and historic floods, the use of GM seeds had transformational effects on the living standards of these poor farmers. Prof. Thomas has also conducted studies of insect resistance white maize, a major food crop for rural black people, that greatly reduced the need for and costs of insect sprays (pesticides) (see Thompson, 2002 for more details).

[47] The two researchers most commonly mentioned who are affiliated with the Biotech Program are Greg Blantch and Rosemary Darlington. ?ck name Dave Woods, one of the pioneers in GMO in agriculture science spent much of academic career at Rhodes.

Prof. Thomson teaches the techniques needed to produce GM seeds to a highly cosmopolitan group of graduate students. Current, a Kenyan and Indian are working with her at her laboratory at UCT. Over several decades Prof. Thompson has taught many foreign students, including the US biowarfare researcher, Stephen Hatfill. She has influenced hundreds more students with her best selling book on GM foods in Africa (2002).

Graduate students, majoring in biochemistry, molecular and cell biology, use her laboratory facilities. She and her students are using gene marker to produce African strains of resistant maize. They are also working on using the genes from the Resurrection Plant, which is indigenous to Cape Town, to produce ordinary drought resistant plants. The Resurrection Plant can dry out to 5 per cent of its normal water level and be returned to normal with water in 80 hours. It grows mostly in the cracks and rocks in the veld area of the Drakenburgs Mountains. The goal is to produce drought resistant soybeans and maize.

2.10c Forestry and Agricultural Biotechnology Institute, University of Pretoria (FABI)

Another research center involved in sophisticated biotechnology research is the Forest and Agricultural Biotechnology Institute (FABI) that is located at the University of Pretoria in the same building that will house the new Bioinformatics Center. Established in 1998, the scientists and students affiliated with FABI speak 28 different languages. This large international student body reflects two trends. First, it is about 20 per cent cheaper to obtain an advanced science degree from a South African university than from a university in the United States. Secondly, FABI has been very successful at obtaining funding from several outside foundations, including Rockefeller, Gates Mellon and Rockefeller. Currently only about a quarter of the international students that attend FABI are advanced graduate students (i.e., M.S. –to-post-doctorates). If all goes well, FABI will have funding for 50 PhD candidates within five years! (Interview with Michael Wingfield, Director of FABI, June 26, 2003).

The following summary of some of the FABI faculty research illustrates how increased numbers of South African and foreign students from Africa and beyond are using near state-of-the-art research methodologies in biotechnology.

FABI's mission is to coordinate and promote biotechnology research and education in forestry and plant science in South African universities. After two years of planning the goal of linking researchers with common interests in DNA and plant biotechnology across several campuses is finally bearing fruit. FABI is actually a suite of departments with faculty coming from a variety of departments, including Plant Production and Microbiology, Agriculture, Botany, Biochemistry Genetics, Entomological and Zoology. Faculty share space, equipment and operate as a lobbying consortium. FABI faculty gave as an example of their coordinated research and lobbying efforts the problem that they current have two mainline sequences and two additional automated sequencers. FABI faculty are now lobbying because they all need another sequencer for their research.

FABI faculty and students also share a 10 million rand grant that is used for student publications and collectively share the services of the only micro array service in the country. Three people run this service. There are biweekly FABI meetings that are attended by about 150 interested persons, a communal email list, and a web page that is used for summarizing new technology (www://up.ac.za/academic/fabi/). Nearly all of the professors affiliated with FABI are working on unique research topics. The FABI researchers interviewed for the study agree unanimously that South Africa's comparative advantage is in pathogens that attack commercial trees. This is a serious issue for forestry industries worldwide since pathogens travel around world. FABI researchers, like most South African university researchers have been successful at developing international collaborations and will continue to seek international collaborations in the future.

Faculty research interests are diverse but centered around common plant and forestry pathogen problems. For example, Prof. Michael Wing field's research group studies various aspects of fungi important to the forestry industry of South Africa. Zander Myburg, a Lecturer in the Department of Genetics is interested in the genetic improvement of Eucalyptus trees via inter-specific hybridization. He is using molecular genetic models to study the differences between Eucalyptus and hybrids. Dr. Altus Viljoen, a microbiologist is working on plant pathogens in four areas: seed plants (i.e. sunflower), banana, the genetic markets that transform fungi, and using tissue culture to isolate resistance genes for banana. Prof. Brenda D Wingfield, Department of Genetics, has worked on the joint Tree Pathology Program (TPTC) since 1989. She heads a group looking at fungal pathogen of plants, Eucalyptus, Pine and alien vegetation. Her group is trying to develop more sophisticated models of how pathogens, particularly fungi that move around the world. She uses DNA-based diagnostic tools to study pathogens and also has a small program to identify genetic disease resistance and how biocontrols can be used to reduce chestnut black fungi on crops. She has also mapped one of the two groups of basic genetic DNA markers in a pine pathogen. She believes that plantation research is a good niche research field for South African researchers, in part because of South Africa's rich biodiversity and because so few researchers are involved in this line of research.

Prof. Dave Berger, an Associate Professor of Botany at the University of Pretoria, is engaged in gene discovery using the micro array facility as a joint venture with CSIR Bio/Chemtek. He is looking at the plant responses to pathogens at the molecular level and providing testing services for local users and researchers at FABI. He is currently training 12 masters through post-doc students in microarray tool discovery and plans to expand the number of graduate students in the program as FABI grows. According to Prof. Berger, FABI is working on developing gene chips using glass slides. The laboratory facilities also have a microscope scanner, and data base analysis. Prof. Berger is playing a key role in developing the U. of Pretoria/ACGT bioinformatics node. FABI's DNA array facility is located in Prof. Berger's laboratory at the U. of Pretoria. More details about the DNA array facility and services available at the University of Pretoria can be found at: http://fabinet.up.ac.za/microarray/. For more information on other faculty affiliated with FABI, see http://www.up.ac.za/academic/fabi/personals/mike.php.

The Director of FABI, Prof. M. Winfield believes the future of FABI and biotechnology research in South Africa is bright. He believes that most GM plant research in Africa will continue to emphasize genome sequencing. However, the service base and number of highly educated scientists in Africa is very low and remains heavily concentrated in South Africa. In fact, ninety per cent of all DNA sequencing that has been done in Africa has occurred in South Africa. While most of the successful work to date has involved international collaboration, this trend has been changing since 1995 when new public funds (i.e., Innovation Funds) became available. Prof. Wingfield believes that South Africa has the potential to maintain "islands of excellence" in terms of graduate studies and research that are on par with first-rate universities in the developed world (Interview Prof. Michael Wingfield and Prof. Brenda Wingfield, FABI, June 26, 2003).

2.11 Biotech Education Initiatives

The third prong of South Africa's biotechnology initiative is public outreach and education. A new program, Public Understanding of Biotechnology (PUB), was funded with R15m ($US1.9) over three years. This program is managed by the Foundation for Education, Science and Technology (FEST), a government entity that falls under the authority of the National Research Foundation. The focus of the new program is genetically modified organism (GMOs). The target audiences are students in secondary schools and consumers. While the program appears on the surface to be a pure education initiative, there was a

great deal of internal debate at FEST about the need to given any attention to "dissident views" within the South African government who are not supportive of GMOs. The arguments of opponents to GMOs will no doubt be represented in the materials prepared for the program science many members of the current government, especially in the Dept. of Environment and Water Affairs, are opposed to GMOs.

In the area of public health research, the Department of Health has stopped funding basic research in pathology. The National Health Laboratory is now a revenue-based organization that must collect most of its revenue from fees at the same time that there is no money for science research. The second problem is that there is no effort to describe what scientists do in practice in school science curriculum. An ill-defined curriculum is aggravated by the lack of coordination across schools or provinces and the lack of money for laboratories. The third problem is the lack of post-doctorate careers in science in South Africa today (Interview with Dr. Wilmot James, July 7, 2003).

2.12 African Genome Project

The first African genome conference was held in Cape Town from March 19-22, 2003. There were 300 participants and five workshops covering such varied topics as Drugs and Vaccine Discovery, Genomic and Post-Genomic, Biotechnology, Education, and Ethics and Law. Welcome Trust, the Swiss Development Corporation and the South African Human Sciences Research Council (HSRC) paid for the conference. The conference was preceded by a workshop on Darwin. Several products from the conference are planned including a book entitled, Genomic and African Society (forthcoming), a new magazine, African Scientists, with a first issue scheduled for September, and a television program that is being produced by the South African Broadcasting Corporation (Interview, Dr. Wilmot James, July 7, 2003).

The two conveners of the conference, Professors Wilmot James of the HSRC and Dr. Wieland Gevers, President of the SA Academy of Science felt the time was right to hold a conference to consider the consequences of the completion of the human genome sequencing project and to identify ways that African researchers can take advantage of the remarkable new biological knowledge and contribute to future research and development in biology.

The conference was so successful that it is scheduled to become an annual event. The second annual conference will be held in Cairo in 2004. The Ain Shams Mutigent Society of Egypt with is the co-convener for the second African Genome Conference. The 2004 conference promises to be a significant networking event between researchers and policy makers in North Africa and sub-Saharan Africa. Historically, Egypt has been more orientated towards the Middle East. However, the choice of venue for the second African Genome Conference was a conscious choice that reflects the desire of the South African government and many academicians to promote greater cooperation and integration among all countries on the African continent.

2.13 Develop capacity and cooperation throughout Africa

While the prevailing view is that there is "nothing" going on related to biotechnology R&D in Africa north of South Africa, this research found some important initiatives underway that are likely to lead to a more coordinated continental-wide capacity to engage in sophisticated biotech research. Moreover, several of the facilities that will form the backbone of future coordinated biotechnology research activities in Africa already exist. This section identifies national, regional, and international initiatives that are likely to increase the human and physical capacity of African nation-states to participate in sophisticated biotech

R&D in the future and identifies some of the existing facilities that are likely to sponsor important R&D activities in the future.

The most important South African initiative likely to increase the capacity of other African countries to engage in sophisticated biotechnology research is the long-term goal of the South African National Bioinformatics Initiative (SANBI). SANBI plans to construct a continental network of computer faculties capable of doing sophisticated biotechnology research. This is an important component of Professor Winston's Hide's vision of what SANBI should accomplish over the next decade (Interview, Prof. Winfree Christie, July 8, 2003). The five-year genomic plan of the African Center for Gene Technology (ACGT) in Guetang shares the SANBI goal of building a continental-wide bioinformatics network. The current phase of ACGT's five-year plan focuses on building capacity for researchers at South African universities and at ARC institutes. However, the next phase of ACGT's work will focus on bringing additional institutions into the bioinformatics network, including research institutes in other African countries.

The current South African vision for a continental bioinformatics network envisions every African country having one or more centers of excellence where sequencing research can occur. Each of the centers will require seed money and computer infrastructure, including dedicated computer lines. Most South African researchers and government officials involved in biotechnology R&D believe that other African countries should develop a coordinated national program similar to one imitated by Brazil to promote domestic biotechnology R&D. Thus, many South Africans are working to establishment regional hubs throughout Africa that are similar to the BRICS and incubators found in South Africa today.

Recent United Nations activities complement or mirror many of the goals found in South Africa's development plans. Several units of the UN have recent called for an increase in the biotechnology and computer capacities of African countries. The establishment of regional bioinformatics centers of excellence was identified as an important goal of the UN Environmental Program at the Cartegena Conference. A Forum on Biosafety, established at the Cartegena Conference, is also supporting the establishment of regional centers that are capable of conducting research on the safety of new GMOs in food products. The city of Nairobi, Kenya has already been selected as the future regional center for Africa.

Establishing national and regional research centers capable of doing sophisticated research is now a priority of several non-governmental organizations and governments who fund development projects in Africa. Several European governments, along with the United States, have increased their financial commitment to help African countries cope with HIV/AIDS and other infectious diseases. Some of this money has already been allocated to developing new medical research facilities that will utilize sophisticated biotechnology techniques. The East African Research Institute at Mekere University in Uganda now has a modern laboratory capable of supporting research in the area of agriculture and environment. Researchers working at the new institute also have access to modern computer facilities at the Hilary Clinton Bioinformatics Computer Laboratory.

Today, there are several research centers that have the laboratory faculties necessary to undertake second or third generation research in Africa. Many of these facilities are run by international organizations affiliated with the United Nations or are national facilities that have been able to improve their facilities with funds from outside donors. The World Health Organization runs a Tropical Disease Research Institute in Tunisia. In Algeria there are no national agricultural institutes doing GM work but there is at least one research project sponsored by CTIGR. Algeria also has a large scientific community that has the training to conduct biotechnology R&D research in the future. Nigeria also has several research institutes, such as CEPEI, and many established university that can serve as the basis for sophisticated biotechnology R&D in the future (Interview, Professor Thomson, Cape Town, July, 10, 2003).

A wider continental view of biotechnology R&D suggests that there is already a great deal of human and physical capacity engaged in biotechnology research in several countries north of South Africa. Today, Egypt is a second major center of biotechnology capacity on the continent. The concentration of biotechnology institutions, expertise, and ongoing R&D activities is the principle reason why the Human Science Resource Council of South African decided to hold the second African Genome Conference in Egypt. The Egyptian co-sponsor of the conference is the Ain Shams Mutigent Society of Egypt (Interview, Dr. Wilmot James, July 7, 2003).

In sharp contrast to the views of many researchers in South Africa and throughout the west who believe that Egypt has very little biotechnology R&D, Professor Jennifer Thomson describes the facilities of several Egyptian institutes as "fantastic." Her role as a senior adviser to the UN Secretary General has allowed her to travels widely throughout Africa. Professor Thomson is impressed by the existing facilities and research programs in Egypt for conducting genetic modified research in the area of plants and agriculture as "fabulous" (Interview, July 10, 2003). She noted that the Agricultural Genetic Engineering Research Institute (AGEDLL), is developing in-house capability to develop and test commercial transgenic crops. The institute either has or will soon have the capabilities to conduct their own field research independent of any outside assistance. The Library of Alexandria has most of the genes currently being used by agricultural researchers working with GMOs. Researchers affiliated with the Alexandria Library are not yet isolating genes but plans to do so are underway as are plans to replace a large company in Bali who currently irrigates 100 per cent of Egyptian crops. Professor Thomson also noted that several universities in Egypt have the facilities to do second or third generation biotechnology R&D (Interview, July 10, 2003). In the area of vaccine production, the one institute outside of South Africa currently producing vaccines for the African market is located in Egypt. The facility, Africa Vacera, is closely affiliated with KlaxoSmithKline (Interview, Dr. Wolf Katz, Biovac Institute, July 8, 2003).

Kenya is another emerging node where biotechnology R&D is emerging. Researchers at several agricultural research institutes in Kenya are conducting R&D using biotechnology techniques on livestock, agriculture GM, and commercial tree farming. The two livestock facilities are Enteynolyist Nairobi and the Kenya Livestock Institute. Researchers affiliated with the International Center for Inspects, Phios and Etiology or Olemoiyoi are also involved in GMO research. Prof. Morris of ACGT found some agriculture research involving genetic modification occurring at the Kemri Medical Research Center. The Kenyan Agricultural Research Institute (KARI) also sponsors several GMO projects.

According to Professor Thomson, the main goal of African agricultural researchers in the future will be to identify the sequence of all viruses that are currently major problems to commercial growers of plant and tree viruses. If Prof. Thomson is correct, a great deal of the biotechnology research in Africa during the next several years will involve field trials of various GMOs developed to cope with several different viruses, such as maize tree virus, that are found primarily in Africa and are cause African farmers major problems.

2.14 Emerging Issues

Several problems mentioned repeatedly by interviewees for this study are likely to figure prominently in the future policy issues and debates in South Africa, within the South African Development Organization, and in future negotiations with the developed world. At the most general level it is important to appreciate that South Africa's biotechnology initiative is viewed as only one of many tools for encouraging a third way or approach towards development. Central themes of the approach is an emphasis on macro-economic growth, poverty reduction, and job creation, especial in science and high tech sectors

of health, industry, and agriculture. Currently, donor countries such as the United States offer event-based or program based assistance programs administered by particular agency programs (i.e., USAID programs). The United States and other developing countries should expect to hear increased number of complaints from recipient African countries in the future.

The US Agency for International Development mission in South Africa views GM seeds as an important tool to help increase food security throughout the Southern African region (Telephone interview, Rick Helms, Agriculture Counselor USDA US Embassy Pretoria June 10, 2003). However, other parties in South African society are increasingly lobbying for more studies to address the fear of the public and concerns of NGOs who are opposed to further introduction of GM substances into the South African food chain. Differences in national policies between the United States and the European Community will increasingly be a matter of concern to South Africa and her neighbors as they attempt to expand their exports to countries in Europe and North America.

The current pattern of vaccine development research in South Africa illustrates the reality that most modern medical research requires international partnerships and cooperation. This transnational cooperation may be useful in terms of building intellectual (and intelligence links) across countries in the developed and developing world. However, it should be recognized that many of South Africa's best researchers feel that they are treated as financially dependent "junior partners." This shared view suggest that there may be a large gap developing among researchers in the developed and developing world in terms of what will be developed and who will benefit. In a world where sophisticated knowledge about how to use 3rd and 4th generation biotechnology is rapidly spreading throughout the world, this knowledge gaps could be the basis for future conflicts between communities of scientists or the basis of grievances of a single disaffected biotechnology scientist who may be willing to use his or her expertise in the future to engage in terrorism for political or personal motives.

2.14b Who owns what: What can be patented in living organisms?

A larger set of looming issues that may form the basis for future conflicts among researchers and companies in developed and developing nation-states revolve around intellectual property laws and patent issues. Several South African researchers complained bitterly to this researcher about how their ideas are stolen by foreign multinational corporation or foreign colleagues. The current practice of patenting sub-licenses and recent efforts to patent processes and procedures in ongoing biological research is already a major issue for many South African scientists. Even well financed HIV/AIDS researchers report that they are finding the high costs of patents, licenses, and sub-licenses to be an increasingly serious constraint in ongoing research.

The issue of who can own what is increasingly important to both university researchers and biotechnology start-up companies in South Africa today, and other developing countries. The main area of concern today centers on the legal rights of different actors pertain to the cost of securing sub-patents and the legal right to patent processes and products before proof of concept is completed. Many issues are also raised by the use of genetic modified organism in agricultural research and the exploitation of indigenous plants. For example, when indigenous plants are commercialized, do indigenous people in the area (or those living elsewhere) deserve a share of the profit? Who will benefit from novel sub-processes that are developed by only one national group within an international collaborative project?

Conflicts may also arise in the future between South Africa and the United States if South Africa expands it's current level of collaboration or sharing of high tech biotechnology procures with nation-states considered to be enemies by the United States. While the United States may not be happy about the current collaborations between South African and Cuban researchers in the area of vaccine development, this line

of collaboration is not likely to set off alarm bells. However, a new biotech agreement between South Africa and Libya to conduct joint research in areas involving bioinformatics or proteomics would be cause for alarm, from the American perspective, due to the possible dual use nature of the research. Thus, the conflicting visions about how to proceed in the realm of regulation and intellectual property protection that are already evident in the two countries are likely to become contentious issues among and between developed and developing nation-states in the future.

Section III
Conclusion and Recommendations

3.0 Summary: Current Civilian Biotechnology Trends in South Africa

South Africa's National Biotechnology Initiative is attempting to re-invigorate a sector that experienced significant declines as large national and multinational corporations reduced their presence, and thus, limited job opportunities in high tech sectors in South Africa over the past decade and a half. While it is too soon to evaluate the effectiveness of the new imitative, most South African researchers were positive about the positive role of the Innovative Fund in stimulating biotechnology R&D in universities and new biotech companies. This same group of researchers doubts the ability of grants from the newly formed Biological Regional Innovation Centers (BRICS) to replace Innovation funding or make up for the lack of funds needed to sustain both basic research and bridge funds to commercialize insights from earlier basic research. Many researchers feel that largely government bureaucrats and recent biotech managers rather than scientists who designed the new program have made unrealistic assumptions about what it takes to maintain research and commercialize biotechnology.

The equivocal evaluations of the BRICS tap a larger problem facing the South African government today. There is a lack of adequate funding for basic research in universities and for science education in South Africa. Many researchers in university research complain bitterly about the disconnect between government officials and bureaucrats who are interested in how fast basic insights can be commercialized and new jobs created and basic researchers whose ability to generate new insights are hampered by measly amounts of research funds available for basic research and graduate education.

Nearly all of the more successful, sophisticated R&D infinitives currently underway in South African universities are international collaborations or research programs that have been able to attract funds from outside donors. These projects are found primarily in the health and agriculture sectors. One of the main findings of this study is that most of the successful, sophisticated biotechnology research projects are international collaborations. This means that in many respects South African researchers are very similar to their peer scientists in western countries. However, most biotech university researchers that have remained in South Africa share a set of values that is focused on improving the conditions under which researchers in the developing world conduct science research. This shared mindset leads many South African researchers to focus on policy issues related to the development of international norms and laws that will safeguard the intellectual property of inventors and investors living in the South.

A similar set of values and beliefs is likely to mean that South African researchers and government officials will play a lead role in efforts to extend the IT rights of researchers in the developing world and to work to expand access and cooperation among African research institutes. The South African Bioinformatics Network Indicatives is the most promising current program that may extend the ability of researchers at modern institutes throughout African to engage in sophisticated bioinformatics research in the near-term future.

University researchers in South Africa will also play influential roles in educating the next generation of scientists and researchers trained in sophisticated biotechnology techniques throughout Africa and the developing world. As the number of biotechnology programs at higher education institute and Technikons expands, South Africa is producing more and more well-trained scientists and technicians. Many of these recently trained individuals will be unable to get jobs in South Africa or in other developing countries. An expanding pool of skilled scientists and technicians chasing a limited number of jobs is a problem that is being replicated in several developing countries today. It is doubtful that current national biotechnology infinitive underway in South Africa will create enough new high tech and unskilled jobs to make a significant dent in unemployment levels in the short-term.

The current size of the private biotechnology sector is very small and consists of probably no more than a couple dozen up to twenty small biotechnology start-up firms. Most of these firms are struggling to find niche markets in the global economy. While the biotechnology used in larger and more established sectors such as mining, wine, and beer are second or third generation, some researchers in health and agriculture are using third generation techniques. A handful of researchers are conducting cutting-edge research in molecular modeling, developing novel drug delivery systems, and new vaccines in South Africa today. The case studies of Synexa, Shimoda, MeyerZall and Biological Control Products illustrated the types of sophisticated cutting edge research that is underway at private biotechnology companies in South Africa today.

One of the most interesting findings of this study was the discovery that many biotechnology start-up companies are conducting their R&D at rented laboratory space at Technikons that were built during the apartheid era for non-whites. Two of the four biotechnology start-up company identified as having some of the most sophisticated and cutting-edge process and products, I.e., Meyer-Zall in George and Shimoda just south of George, are both renting laboratory bench space at underutilized “Technikon” that were built during apartheid as showcase technical colleges where bright non-white South Africans could learn to become technicians for science and industry. Many of the Technikons, including the George campus of the Port Elizabeth Technicon located near former President P.W. Botha’s current home, are well-kept, contain lots of empty lab spaces, and are perfect out-of-the-way location for private companies who are working on proof-of-concept and other pre-patented research stages.

The importance of Technikons as venues for innovative private R&D and for education is likely to increase in South Africa over time. As a study designed to study the feasibility of a new biotechnology hub along the Garden Route Corridor near George recently noted, “the profiles of the postgraduate students are changing…. Technikons are enrolling more post-graduate from disciplines such as Microbiology, Food Science, Marketing, and Pharmacy.” If present trends continue, many of the future graduate students are likely to come from other countries. The report went on to note that the PE Technikon at George was especially desirable since it already had “a well-established network with a number of institutions and companies including: University of Pretoria, University of Stellenbosch, Intervet, Bayer, Virbac, Syngenta, Mosstrich, Chemistry Department of Port Elizabeth Technikon, Western Cape Government Department of Agriculture, Embrapa (Brazil), Veterinary Institute at the Tel Aviv School of Medicine, CIRAD, MeyerZall Laboratories and the Agricultural Research Council. (Idea to Industry, 2002, p. 8).

This trend of having some of the most novel R&D programs being conducted on a “shoe string budget” at out-of the way scientific laboratories in technical schools may be the more important finding of this project because it suggests how difficult it will be in the future to monitor biotechnology R&D trends in developing countries as the size of the pool of scientific and biotechnologically educated researchers increases in future decades. Today, the poll of qualified researchers is still quite small in South Africa and it is relatively easy to locate where private R&D research is occurring. However, as the number of biotechnology start-up firms using bench space at Technicians or other undisclosed locations grows, the

monitoring process will become more challenging. The tendency for an increasing number of small R&D shops to set up shop at more and more out-of-the-way locations, such as the Technikons of South Africa, is likely to become an increasingly common pattern in other developing countries in future decades.

3.1 Conclusions

This study reached five conclusions that may be relevant for understanding future biotechnology trends throughout the South.

1) First, there is *no evidence that the South African government is engaged in covert biological warfare research*. Any covert state-sponsored research activities are likely to be minimal efforts to keep up with current research trends at institutions that conducted secret bio-chem research in the past. The most likely candidates for hosting minimal R&D include the public-private entity, Protechnik, and one or more research units (e.g., the Foot-and-Mouth Disease Institute) affiliated with Onderstepoort, the state veterinary pathology lab and animal vaccine development institute. The probability that anything more than literature surveys of trends relevant to biowarfare research is on going is very low because of the political orientation and resource constraints facing senior political officials in the South African government.

After a decade of majority rule, the senior management of most public and public-private institutions is individuals whose appointment was due at least to some extent to the fact that they will be loyal to the ANC political leadership of the South African government. It would be difficult, but not impossible, for the current South African government to maintain any more than a small, covert biowarfare R&D program or engage in secret work with other countries without these activities leaking to the public in the new South Africa.

Instead, organizations such as Protechnik, that were involved in past covert chem-weapons research, now provides the technical support, including the services of a full-time microbiologist, to support the work of a Cabinet level Committee on Weapons of Mass Destruction (WMC). The WMC committee is tasked with implementing the South African Weapons of Mass Destruction Act considered by many to be among the most ambitious non-proliferation national legislation in existence. Members of the WMD committee are appointed by the Cabinet to represent several different cabinet agencies and sectors of South Africa economy, including the civilian biotech sector. The WMC Committee reports directly to the President and is responsible for conducting inspections at all public or private sites that are capable of producing chem-bio biotech products. The urgency for establishing national protocols for WMD inspections at biological entities lessened with the collapse of the Verification Protocol talks of the Biological Warfare Convention last year. However, the WMD committee plans to continue inspections of public and private institutions capable of producing chem-bio warfare products, in addition to monitoring exports as well as imports of international recognized biological and chemical controlled chemical and biological substances.

2) Secondly, the *probability that one or a few individuals in the private sector could be engaged in sophisticated biowarfare research in South Africa today without detection is also low*. South Africa is no longer an attractive location for sophisticated efforts to develop biological agents for political warfare or terrorism because most members of the business and scientific communities accept the idea that biowarfare research is an activity that is better left buried in the past. The small size of the scientific community and the high level of integration of South Africa's scientific and biotech communities into western science and commerce further ensures that most secret efforts, especially large-scale or costly research and development programs, within private corporations would become known to other researchers. There was unanimous agreement among the experts interviewed for this study that any *widespread use o sophisticated dual use R&D would be quickly detected by members of the scientific-biotech communities and reported to*

government authorities. While it might take longer, several non-government organizations such as SAAVI or BioWatch would also be likely to hear and report rumors of suspicious activities. However, the large size of the country combined with the high standards of living, first-world transportation infrastructure, and pool of experienced biowarfare scientists who are having trouble making financial ends meet, means that several locations in South Africa remain highly attractive locations for smaller scale, "bush laboratory" facilities.

The fact that three researchers were able to surprise the local and international community in 2003 by cloning a cow using a hand-cranked generator on a rural farm in South Africa should sound a loud warning about the type of sophisticated research that can be current be conducted on a shoe-string budget in rural parts of developing countries. Moreover, there is a very real possibility that a small group of researchers, including former Project Coast scientists, a few left-ring or right wing political dissidents, a dissident biowarfare or civilian biotech researcher, or terrorist groups may attempt to use their biowarfare expertise for personal gain or political motives.

3) Third, there was unanimous agreement among the interviewees for the study that it would be next to *impossible to detect the activities of a small, and committed private secret biowarfare effort that operated in remote areas of South Africa or in neighboring countries* (e.g., the Democratic Republic of Congo). Most interviewees thought that such an undertaking would only be discovered if the goal was to produce large quantities of an agent for mass destruction. Nearly all of the experts interviewed felt that most *terrorists, except for the lone individual with advanced training in civilian biotech R&D, were most likely to use readily available biological pathogens that were endemic to the area and that require little or no processing.* Several respondents mentioned hoof-and-mouth disease as a likely agent to be used in future terrorist attacks since it can easily be distributed and can cause widespread disruption and some deaths.

Nearly all South African plant biologists are working hard to commercialize some aspect of the natural biodiversity found in South Africa. This trends means that several researchers have the technical expertise and materials to produce new, exotic bioterrorist weapons. In South Africa there is a virtual cottage industry developing to exploit indigenous plants. Many of these researcher are working at out-of-the-way locations alone or with a very few associate or are located in academic departments that are not normally associated with biowarfare. Thus, while the University of Cape Town Zoologist won't turn out big science, their work on abalone is highly innovative (J. Thompson, UCT, July 10, 2003). However, most plant biologists believe that the education needed to do innovative research is more difficult than physics and require knowledge of advanced math.

4) Fourth, *South Africa will continue to be an important "hub" for biotech R&D activities in Africa and the developing world for several decades*. Although the size of South Africa's biotech civilian sector is miniscule compared to the United States or Europe, there are a few pockets of novel third and forth biotechnology R&D in the country. In vaccine research, several university-affiliated research groups are working on novel approaches to vaccine development. Many of these South African researchers are working in collaboration with researchers in the U.S. and Europe, including several who are currently working with researchers at the National Institute for Health. Only a few private start-up companies in South Africa (e.g., Shimodu and MeyerZall) who have developed drug delivery systems that are novel ways to delivery drugs, or any pathogenic agents, to targeted cells. Moreover, the South African government's Biotech Initiative will continue to expand the human and physical capacity needed for future sophisticated biotech R&D. Increased public money is helping to spur more opportunities for graduate level education in biology and related fields.

A new nation-wide National Bioinformatics Initiative that will link major research institutes into a computer network is also being developed. The South African National Bioinformatics Initiative (SANBI) is designed to facilitate more collaboration and to provide greater access to sophisticated bioinformatics

computing capabilities and gene libraries. These recent developments suggest that South Africa will be an important locus of advanced training and research in the developing world for decades. At least five world-class research universities in South Africa train individuals from more than 20 different countries in state-of-the art biotech R&D techniques today.

5) Fifth, a rudimentary network of research institutes that are capable of doing sophisticated biotechnology research already exists throughout Africa. *As South Africa's National Bioinformatics expands, the capabilities necessary for more sophisticated biotechnology research to proceed at "islands of excellence" throughout the continent will also grow*.

3.2 Recommendations

#1 The USG should make modest strategic investments in biotechnology start-up companies and university research programs in South Africa and other developing countries.

The study recommends that the USG make some modest strategic investments in promising private start-up biotech companies while also establishing new research partnerships between DOD researchers with researchers at a couple of South African universities involved in sophisticated biotech research in each region of the developing world because this approach is probably the most effective and cost efficient way to monitor potential dual use biotechnology capabilities in developing countries. Modest strategic investments in South Africa could be made in a couple of the biotechnology start-up companies conducting research at Technikons in South Africa, such as Shimoda or MeyerZall. Shimoda by all accounts has the most potentially most lucrative and novel drug delivery system. However, Shimoda already has several international partners. MeyerZall, on the other hand, is currently working with the main supplier of vaccines to the government, BioVac. Only a few large investors, including Haber, a state-run research institute in Cuba are currently funding BioVac's operations. Another company that is pursuing an innovative technology using a membrane bioreactor for various industrial applications, in addition to pursuing AIDS and cancer research is Synexa Life Sciences. A third investment in a private company like Biological Control Products would provide access to key knowledge about customers using microbicides for pest control throughout Africa and the Middle East. Since there are still only a few middle-level nation-states who are economically developed enough to be supporting sophisticated biotechnology R&D regions outside of the US, Europe and Asia today, 10-to-12 corporate investments or collaborative research projects with researchers at key universities in critical countries in each developing region of the world may be the optimal approach for monitoring future trends in biotech research and graduate training throughout the developing world.

#2 Increase collaboration between USG DOD/Intel agencies and NICD.

Today South Africa serves as a key node for the surveillance and management of infectious diereses for the entire African continent. The South African National Center for Infectious Diseases, similar to the Center for Disease Control in the U.S., is responsible for surveillance and management of infectious diseases for the entire African continent. The *NCID BSL-4 lab routinely analyzes specimens from African countries and from other developing countries as far away as Pakistan*.

The information and contacts available by working with NICD are likely to become important in the future as more people gain competency in biotechnology that can be used for military or terror purposes. While the NICD has no formal interactions with private companies, actors in the private sector are expected

to provide "good will statutory notification" when they are working with infectious agents or encounter possible infectious disease agents. However, there is no enforcement mechanism in place to monitor the activities of biotechnology start-up companies or to hold them accountable in terms of notification requirements or norms. Thus, it may be a wise practice to support new cooperative activities with NICD in the areas of early warning, diagnostic procedures, and research on infectious diseases with relevant DOD entities, in addition to continuing current collaborations with researchers at NIH.

The strategic importance of NICD as the central diagnostic center in Africa for infectious diseases is obvious. Long-term professionals such as Dr. Schoub and his associate, Dr. Bob Swanepoel, are among the most knowledgeable medical researchers of infectious diseases found in Africa, in addition to have a great deal of experience working to diagnose and clinically manage old and emerging infectious disease using ad hoc communication systems. The increased number of emerging diseases being brought into the United States in recent years suggests the importance of increasing collaboration with the NICD in the areas of disease surveillance and targeted vaccine research.

Less apparent from the mission statement of the NICD but of potential value under certain circumstances is the central role that NICD personnel can play as a source of information about human activities related to possible biowarfare activities in the future. Dr. Schoub came to the institute in the late 1970s at the time when one of his contemporaries, Dr Woulter Basson (AKA Dr. Death), was completing his master thesis in medical virology at the institute. Dr. Swanepoel, the most senior NICD's infectious disease specialist, is a highly effective and credible microbiologist today in part because he is one of the few microbiologists who worked for the government under apartheid who did not get involved in secret biowarfare research. These two individuals have by virtue of their past experiences, contacts, and reputation access to a great deal of information about what is going on with infectious diseases in South Africa and throughout the continent. Dr. Swanepoel, for example, is on an International Board for BioDefense and frequently consults with governments from such diverse areas of the world as Africa and Eastern Europe.

USG collaborations with South African National Center for Infectious Diseases (NCID). NCID is a key South African institution could also be a valuable relationship in future efforts to identify the source and to manage world-wide outbreaks of infectious diseases. NCID also has an impressive network of professional contacts that it taps to run ad hoc cooperative programs such as during the recent scare of a possible SARS epidemic hitting the continent. The personnel are used to dealing with the need to contain the most infectious diseases in several countries under adverse conditions and the NCID also has a specimen culture library dating back to the 1970s.

#3 Require an annual or biannual inter-agency state of civilian and dual use biotechnology trends in the world.

A third recommendation is for the USG to require a new annual or biannual inter-agency status update report about key biotechnology trends in the public and private sectors of the targeted nation-states for each region. This recommendation is based on the fact that the US government employees who were best informed about current potential dual use biotechnology activities were Science Officers at the State Department or worked for USAID rather than DOD or in political positions at the State Department. By expanding the membership on a standing inter-agency task force assigned to survey recent trends in civilian biotechnology with potential dual use applications to include representatives from Agriculture, Energy, and Environmental affairs, in addition to political and science officers from State, DOD, Commerce, USAID and other executive agencies, the US is more likely to obtain a complete picture of emerging biological dual use trends in the developing world.

#4 Send USG representatives to the March 2004 African Genome Conference in Cairo, Egypt.

The fourth recommendation is to send a couple of USG representatives to the 2004 African Genome Conference in Cairo. US representation at the second African Genome Conference would be an extremely economical way to identify key individuals and biotech trends throughout the continent.

More details and additional policy recommendations about how to monitor biotechnology trends throughout the developing world in different sectors (i.e., agriculture, medical research, industry) can be obtained by consulting further with individuals who were interviewed or identified during this research project as key individuals involved with or knowledgeable about civilian biotechnology trends in South Africa. Appendix A lists key individual and contact information.

#5 *Require all public and private Biosafety laboratories to meet internationally accepted Good Laboratory Practices (GPL). Those that do not the meet should be the target of national or possibly even international inspection.*

The recommendation was made by Dr. Daan Goosen, a former Project Coast scientists, during an interview with the author in June, 2003. For Dr. Goosen, "open transparency and freedom of information are the key way to control biowarfare threats" at the scientific level. His recommendation for monitoring the civilian biotechnology sector is to "get more countries in the developing world on international laboratory standards" used by the United States, the EU, and the OECD. South Africa has a similar body that regulates Good Laboratory Practices (GLP) called the South African National Accreditation Service. This accreditation body certifies GLP based on an internationally recognized standard. The GLP systems of accreditation and regulation are based on "good faith" voluntary compliance so any lab that is not in compliance would be easier to spot once more countries adopted existing standards of accreditation and certification. While the approach does not address the problem of the "lab in the suburbs" or the bush, a focus on accrediting laboratories may be particularly well suited for developing countries such as South Africa where the number of public projects and private start-up biotechnology companies are still relatively small and where everyone seems to know what other biotechnology researchers are doing.

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ARC-Onderstepoort Veterinary Institute (ARC-OVI) http://www.ovi.ac.za/

Exotic Diseases Division. http://www.ovi.ac.za/main/divisions/edd.htm

Biotechnology Partnership for Africa's Development http://www.BioPAD.org.za

Biowatch South Africa http://www.biowatch.org.za/about.htm
A national non-governmental organization dedicated to publishing, monitoring and researching issues of biological diversity, genetic engineering, and sustainable livelihoods.

Council for Science and Industrial Research, CSIR www.csir.co.za

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The Innovation Fund http://www.dacst.gov.za/science_technology/innovation/index.htm

Mbuyu Biotech (Pty) Ltd (A new joint venture between CSIR and BioVenture) www.mbuyu.co.za

Medical Control Council of South Africa http://www.mccza.com/
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Protechnik Laboratories (Pty) Ltd. http://www.sadid.co.za/SADID_7/edition7/protechnik/protechnik.html

South African National Bioinformatics Institute http://www.sanbi.ac.za

South African AIDS Vaccine Initiative (SAAVI) http://www.saavi.org.za/University A network of researchers lining various centers of research excellence and information on ongoing SAAVI Clinical Trials at Cape Town. South Africans for the Abolition of Vivisection (SAAV) Box 3018, Honeydew, 2040

Relevant statutes and government reports:

National Biotechnology Strategy
http://www.dst.gov.za/programmes/biodiversity/biotechnology.htm
National Department of Agriculture Genetically Modified Organisms Act http://www.nda.agric.za/
Non-Proliferation of Non-Destruction Act http://www.gov.za/gazette/acts/1993/a87-93.pdf

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Other African Web Sites

Agricultural Genetic Engineering Research Institute, Egypt
http://www.ageri.sci.eg/

East African Regional Network of Biotechnology (BIO-EARN)
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Science in Africa – jobs in biological sciences http://www.scienceinafrica.co.za/Jobs/biol.htm#1