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The Biotechnology Toolkit

Thomas Alva Edison famously declared: “Genius is one percent inspiration and 99 percent perspiration.” As in Edison’s time, it takes an enormous commitment of effort from inventors to take on the great challenges of the 21st century for development of environmental remediation technologies, cleaner (and cheaper) energy, genetically engineered (GE) products to ensure availability and affordability of higher-quality food, and new, innovative medical therapies, vaccines and cures we need to keep public health threats at bay. Biotechnology entrepreneurs frequently combine a nearly irrational level of optimism, faith, and hard work. Despite the long and sometimes tangled path from the laboratory to the market, pioneering bio-preneurs continue to undertake the hard, unremitting work needed to overcome obstacles on the long path to eventual success.

Key elements in the enabling environment needed to bring life science inventions from the laboratory to the market include:

- Support for basic science literacy and research
- Access to early capital
- An enabling legal framework
- Well-functioning, transparent and science-based regulatory policies
- Market-based incentives for continuing investment in life sciences
- “Doing-business” skill and acumen

Fortunately, we don’t have to know what drives innovators to tackle nearly impossible challenges, only to recognize the value to society of their contributions, and to identify and implement the policies needed to support their continued efforts. This paper seeks to advance this effort, by outlining the policy elements proven to support an enabling environment for commercialization of science in the United States and around the world.

The Core Elements

Support for basic science literacy and research

In the 21st century, no country or region has a monopoly on good ideas. In the United States, leadership in commercial science and technology relies heavily on the durable

support of local, state, and federal governments for continuing science education, basic scientific research, and related infrastructure. Basic science generally is understood to include the study of fundamental science principles and exploration of theoretical or foundational science issues that can lead to breakthroughs in applied research or new science platforms for innovative product development. Support for basic science at the primary and secondary school level starts with science literacy, and includes continuing support for science education and infrastructure in universities and private and public research institutes. Both developing and developed countries need to prioritize support for basic science, which can come from domestic resources or through bilateral or multilateral flows.

Absent government support for science research and infrastructure, provided either by host governments or donors, inadequate financial support for ongoing basic research may pose a major barrier to the spin-off of biotechnology companies by inventors. Basic research may be delayed or interrupted for a variety of reasons relating to grant opportunities, availability of infrastructure like laboratory facilities or other expensive equipment, and appropriately trained scientists and staff. In many cases, lacking funding for forward movement on an important breakthrough, the inventor may be forced to move on to a new area of research, resulting in delay or loss of potential social or economic benefits from the applied research.

At the university or research institute level, support for effective Technology Transfer Offices (TTOs) also plays an important role. In specific cases, TTOs may prove critical to the successful “spinning-off” of biotech start-ups by academic inventors. TTOs play an important role in assisting academic researchers in the identification of commercially valuable science for translation into the marketplace, as well as in the technical process of applying for patent protection and assisting with licensing and other aspects of early-stage commercialization. For example, the country of Chile is now a formidable competitor in innovative agricultural life sciences. Based on the strength of publicly supported research protected by patents and spun out of institutions like the University of Concepcion’s TTO and Fundacion Chile, industry has developed highly competitive technologies in the areas of genetically engineered timber, as well as new agricultural and aquaculture (fisheries) products.

More broadly, biotechnology companies tend to form “clusters” around universities and research institutions to benefit from the critical mass of publicly supported science. This clustering has proven important for generations of longer-term economic and social benefit at the local, regional or national level. Within the United States, California and Massachusetts continue to lead in investments in science education and infrastructure at public and private colleges and universities alike. By attracting and encouraging spin-off of biotechnology startups based on new technologies developed within universities and research institutions, they have become leading life sciences clusters. Smaller biotechs, in turn, have attracted larger, established innovative companies to set up R&D facilities that benefit from the science and technology spill-over. Over time these policies have contributed to vibrant life sciences sectors and continuing innovation successes. In recent years, the greater Philadelphia area in Pennsylvania has risen to second place in the rankings and in terms of rates of high-tech job creation, as documented by the

Milken Institute.¹ Recognizing the power of clusters, India's Department of Science and Technology (DST) provides a targeted support program to establish and expand innovative life science clusters through the "Promoting Industry Clusters (PIC) Projects."²

Access to early capital

Academic researchers and collaborators face a second critical hurdle, namely gaining access to capital to fund translational, early-stage research. Due to the long time periods needed to bring an invention from the laboratory bench to the market, and also simply due to the high risk of failure for early-stage biotechnology companies, biotech remains one of the highest-risk segments in the venture finance spectrum. During the current global financial crisis (2008 – 2009), young life science faces ever-greater challenges in ensuring adequate streams of financial support.

Access to financing may be a particular challenge for academics located in geographically remote locations that are far from life science clusters and related venture finance opportunities. Academic and/or other researchers in developing countries with less well-developed capital markets also face particular challenges in gaining financial support for everything from the patent filing process to translational research and commercial development. In this context, the need for government incentives for venture finance is widely recognized. This support may include tax credits or other incentives to encourage this high-risk lending.

Traditional venture capital firms and so-called angel investors provide capital to early stage companies in return for substantial equity stakes and, in most cases, a say in the management of the company. In recent years, new models of private finance for early stage life sciences companies have emerged, including venture philanthropies, foundations, public-private partnerships (PPPs), non-profit, non-government organizations like the Institute for One World Health (IOWH), and other hybrid models that take into account the nexus between private sector and public sector priorities. In addition, governments in developed and developing states increasingly recognize the need to 'prime the pump.' Programs along these lines include the Small Business Innovation Research (SBIR) program, Cooperative Research and Development Agreements (CRADAs), and others that provide additional grants, soft-loans, or other research assistance to academics and entrepreneurs at the early stages of life sciences R&D. At the end of the day, individual companies may take untraditional routes to raise needed capital for pre-clinical and clinical development (see Box 1, p. 4).

¹<http://www.milkeninstitute.org/publications/publications.taf?function=detail&ID=38801196&cat=ResRep>

² Carried out by the Micro and Small Medium Enterprise (MSME) Foundation, the Indian Department of Science and Technology's (DST) "Promoting Industry Clusters (PIC) Project," seeks to encourage life science clusters in the Hyderabad and Ahmedabad-Vadodara areas. See http://www.msme.foundation.org/Msme_Project.aspx.

Box 1. **Arc Pharmaceuticals Medical Device to Prevent Surgical Adhesions**

ARC Pharmaceuticals Inc. (“ARC”) develops innovative medical devices for the prevention and treatment of surgical adhesions, a major and painful complication of common surgical procedures. As a small life-sciences company located at the extreme western edge of Canada, with limited access to venture financing, ARC developed an innovative business strategy of initially seeking marketing approval for the veterinary market. By first clearing the lower regulatory hurdles for veterinary approval of their lead compound, known as ARCADÔ Instillate, they were then able to use data from the use of the product in animals as part of the required pre-clinical research. To date, ARC been able to demonstrate that the compound is safe and effective in equine clinical trials for the prevention of surgical adhesions. Now with a continuing stream of income from veterinary uses, ARC has more of the resources needed for expensive, time-consuming human clinical research. ARC has also commenced exploration of the use of the ARCADÔ technology in other disease indications and has formulated ARCADÔ as a gel and as a film.³

An enabling legal framework

“Rule of law” protections are critical to an enabling legal environment for bio-preneurs. These include basic legal protections such as freedom to contract, access to the courts and alternative dispute resolution, and intellectual property protections (IPP). Perhaps more than other high-technology sectors, commercialization of life sciences inventions is extremely dependent on IPP, including patents and trade secrets.⁴ These IP assets are valued in the market over the course of many years of R&D and product development that may ultimately cost hundreds of millions of dollars, and in fact may be a small biotech company’s only commercial assets. Trade secrecy also is playing an ever more important role in technology transfer and commercial development of new, innovative biotechnology products.

In 2006, the Milken Institute published a highly influential ranking of domestic U.S. and foreign research institutions in terms of success in life sciences commercialization. This report identified the key role of Technology Transfer Offices (TTOs), predicting success for successful commercialization based in large part on the track record for licensing of life sciences patents by inventors with support of University TTOs.⁵ This and other related research underscores the importance of clear and uniform policies governing patent title for inventions arising out of government funded research as a major driver of

³ <http://www.arcpharma.com/index.php>

⁴ For a more detailed description of the value of IP in life sciences R&D, please download the BayhDole25 IP Toolkit available at <http://www.bayhdole25.org/node/1519>.

⁵ Milken Institute, “Mind to Market: A Global Analysis of University Biotechnology Transfer and Commercialization,” <http://www.milkeninstitute.org/publications/publications.taf?function=detail&ID=576&cat=ResRep>.

commercial development of science breakthroughs in the United States and abroad. The general legislative framework to encourage private sector development of publicly funded research is known familiarly by one of its major elements, the Bayh-Dole Act, and has been emulated by both developed and developing countries.⁶

The vast majority of patents granted (and related trade secrets) never make it to the market, due to the unpredictable nature of applied science. In this context, the large numbers of patents generated every year in the United States are critical in the technology transfer system as a market mechanism that biotech start-ups, universities, and others use to generate licensing revenues and raise money for further R&D. In addition, under U.S. law, most patent applications are made public within 18 months after filing. Following publication, the patent application is available to the general public, along with the entire file history of the application. Accordingly, the process of patenting makes an important contribution to the progress of science and the knowledge base available to researchers around the world.

Well-functioning, transparent and science-based regulatory policies

Regulatory bodies, responsible for oversight of the life sciences industry and approval of new products, carry a weighty burden in developed and developing countries alike. Biotechnology products that either may be consumed directly by people or animals or otherwise released into the environment must meet rigorous health and safety standards. It is critical for long term development of new life sciences products that regulatory systems are effective at evaluating safety and efficacy of new products and are perceived by the general public as able to carry out this critical role. Such regulatory systems must be considered “functioning”, meaning they are science- and risk-based, with clearly defined timelines and processes for regulatory review and decision-making, and appropriate protection for proprietary information and data. The regulatory and decision-making processes must be predictable, completed in a timely manner, and not subject to political influence.

In terms of the evaluation and approval of new products based on life sciences inventions, after a biotechnology company has developed its science platform, recruited management, gained access to capital, and overcome any other hurdles, the hard work begins. On average, it may take a company ten, twelve years of research, or more—including field trials in the case of agricultural biotechnology or clinical research in the case of medical therapies or technologies—to develop the dossier of safety and efficacy data needed for regulatory review. Innovative life science companies therefore rely on well-functioning regulatory bodies with science-based policies to provide consistent, predictable, and transparent outcomes, both domestically and in important export markets.

⁶ For a general review of the development of the Bayh-Dole Act and related policies, see <http://www.bayhdole25.org/whitepaper>.

In this context, regulatory approval of environmental bio-remediation and other green technologies may be extremely difficult in light of the need for a high degree of certainty with respect to safety and efficacy. In fact, the first genetically engineered (GE) organism, Dr. Ananda Chakrabarty's modified oil-eating bacterium, derived from the *Pseudomonas* genus and designed to address the problem of oil spills, while developed commercially, was never approved for open release into waterways in light of concerns about its long term environmental impact.

More generally, commercial development of environmental bio-remediation technologies and genetically engineered plant products, in particular, have been affected by largely non-science concerns arising out of the failure to communicate effectively on science policy in developed and developing countries. When biotechnology policy is not based on objective science criteria, however, vulnerable populations around the world suffer disproportionately. Even in this difficult external environment, notable successes include development of beta-carotene rice (Golden Rice)⁷ and now GE bananas (see Box 2, below).

Box 2. Combating Threats to Bananas in Africa Via GE Varieties

For over 400 million people in the developing world, from Honduras and Cuba to Uganda, Ethiopia, and the Philippines, the banana and plantain are major food staples. 9 of 10 bananas and plantains are consumed in developing countries—90 million metric tons annually—making bananas the world's fourth most important food crop after rice, wheat, and maize.

Due to susceptibility of bananas to disease, crop yields for small-scale farmers are down by as much as 50 to 75 percent in the last 30 years. In Uganda, cultivation of bananas is threatened by fungal disease. Fortunately, a number of government and non-government research institutes in Australia, Belgium, and Uganda, among others, are working hard on GE bananas, which may hold the key to continued production and prevention of hunger in the developing world. Unfortunately, non-science based policies in Uganda have created an anti-GE backlash, delaying the documented benefits the country stands to gain from GE bananas.⁸

Market-based incentives for continuing investment in life sciences

One of the explanations given for the greater relative success of the United States in generating thriving biotechnology clusters is the “high-risk, high-reward” business model. In fact the innovative life sciences products and services developed by companies in the United States create social and economic benefits for consumers and patients in both developing and developed countries.

⁷ The BayhDole25 IP Toolkit provides a brief overview of the successful development of Golden Rice, available at <http://www.bayhdole25.org/node/1519>.

⁸ See <http://www.ifpri.org/pubs/dp/ifpridp00767.asp>

However, it is also the case that the prevalence of price controls for biotechnology products, particularly in the area of healthcare, may tend to artificially reduce global R&D efforts needed to find new therapies and cures for public health threats. In this context, it is important for governments to provide social safety nets that provide access to medicines and at the same time reward, and do not penalize, innovative medical devices, therapies and cures.

“Doing Business” Skill and Acumen

Good science is a necessary but not sufficient condition for commercial success in biotechnology. Time after time, it is the business acumen of the company’s management team that makes the difference between survival and failure of the company.

As noted previously, in many cases the initial science lead that forms the basis for a company’s business plan will fail to reach the product development phase. This is a necessary outcome given stringent regulatory requirements for proof of safety and efficacy for highly regulated biotechnology products. However, it does mean that a successful company is one that is nimble and able to shift the business model to steer away from icebergs and not into them. For this reason, one of the watchwords of biotechnology is that if you are going to fail in pursuit of a particular molecular target, fail early. (See Box 3, below)

Box 3. Overcoming Early Failure in Bio-Pharmaceutical R&D

Alexion Pharma provides a Cinderella story of a company launched in 1992 that until 2007 had not launched a single successful product or achieved any revenue stream, and yet managed to continue operations through the doing-business skills and acumen of its senior management team. Beginning in the early 1990s, Alexion serially pursued and abandoned a lead compound in different therapeutic categories before finally reaching the finish line in 2007 with the highly successful launch of Soliris®, a first-in class innovative therapy providing the first effective therapy for an ultra-rare blood disorder known as Paroxysmal nocturnal hemoglobinuria, or PNH.

Alexion Pharma was the first to discover and develop recombinant complement inhibitor into a viable pharmaceutical product, converting the basic science into an investigational drug and navigating considerable hurdles involved in conducting clinical trials in an ultra rare disorder. It is likely that it was Alexion’s earlier, less successful efforts that contributed to its ultimate success. In the process, Alexion became the first company to have a product receive both regulatory approvals in the United States on a prior review basis and in Europe under Accelerated Assessment, and in 2009 received special recognition with the Prix Galien award in France for the most innovative therapy for a rare disease. Alexion Pharma started to move out of the red in 2008, and in 2009 has continued to expand sales, enter new markets, and explore additional indications for Soliris®.⁹

⁹ For more background on Alexion Pharma, see <http://www.alexionpharm.com/>.

In the health care area, for example, innovative bio-pharmaceutical start-ups nearly always are based on interesting and important science breakthroughs. Yet few succeed. That is why the pre-clinical and clinical processes are referred to, in all seriousness, as “the valley of death.” In the rare cases of commercial success, even fewer companies reach the market with their first priority compound. In other words, the question of whether a new biotechnology company will survive and thrive depends on a nimble business strategy to ensure backup of the priority compound(s).

University consortia, industry organizations, and state and local governments may all provide assistance to scientists and fledgling entrepreneurs to assist them in gaining needed business skills. In this context, alumni of major pharmaceutical and bio-pharmaceutical companies continue to provide the “DNA” for innumerable smaller companies, and remain an important asset for biotech start-ups.