Ensuring Global Access through Effective IP Management: Strategies of Product-Development Partnerships

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ABSTRACT

In the last decade, product development partnerships (PDPs) have become significant components of efforts to develop and disseminate therapies for diseases in the developing world. PDPs seek to fill a gap left by the private sector—a gap that leaves 90% of the world's disease burden with only 10% of the world's research money—through innovative, comprehensive partnership strategies that tap into the strengths of both the private and public sectors. This chapter, based on the proceedings of a conference titled Ensuring Global Access through Effective Management of Intellectual Property in 2006, provides an overview of the history and approaches of numerous PDPs. The chapter is anchored by reports from eight different PDPs and aims toward explaining what potential problems to guard against, what does not work, and—above all what does work—when the public sector plugs into the dynamism of the private sector to try to meet the health and agricultural needs of developing countries. Recognizing that there is no single business model, PDPs employ a common toolbox to manage intellectual property for global health outcomes. It includes defining a discrete territorial market; establishing distinct structures for public sector and private sector markets; determining field of use in a strategic manner; establishing royalty rates to optimize incentives; and providing for access to the developed technology in the event that the research/industry partner abandons the project. Other key areas of discussion, where parallels between PDPs exist, include global-access strategies, pricing issues, the importance of market segmentation, production capacity, strategic early-stage licensing, the IP landscape, and systemic challenges. Collectively, PDPs have broadened the creative understanding of practical ways to resolve the public-policy dilemma of balancing private incentives to generate needed R&D investment with the goal of access to those in need.

1. INTRODUCTION

Infectious diseases such as HIV/AIDS, tuberculosis (TB), and malaria are among the world's leading killers, affecting the poorest people in the most impoverished countries. Yet affordable and accessible interventions are frequently unavailable to them. Moreover, neglected diseases such as leishmaniasis and Chagas' disease kill or disable millions of people in the developing world every year. Treatment options for these diseases are either inadequate or nonexistent because of a lack of public funds and private sector incentive to research and develop new drugs and vaccines. This lack of R&D has created what some call the 10/90 gap; less than 10% of global health R&D spending worldwide is focused on diseases or conditions that account for 90% of the world's disease burden.[1]

Focusing science and technology innovation on tackling these diseases is a necessary, but not sufficient, condition for progress. Improving global health will also require concerted efforts by academic and industrial scientists, technology developers, IP (intellectual property) experts, investors, government officials, policy-makers, and public-health officials. Partnerships are needed, not only to develop the products and strategies for delivering interventions to populations most in need, but also to forge IP and technology transfer agreements that will protect private

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interests while simultaneously promoting public health. Mahoney and Morel have named this new era, "the Era of Partnerships."[2] They argue for an innovation framework having six components:

1. Development and expansion of national health delivery systems, including an attractive, domestic, private-sector market for health products
2. Development of manufacturing capability for health products
3. Development of a drug and vaccine regulatory system
4. Development of an IP regulatory system
5. Development of R&D capability by the public and private sectors
6. Development of international trade systems for health products, including global procurement funds

The authors note that the components are comprehensive in that they cover all the areas necessary to innovate successfully.[3] All of the components are dynamically linked and attention to all is required, since the failure of one component will almost certainly guarantee failure for the whole effort. Thus, though the IP system is only one component of innovation, it is a necessary component. Product development partnerships (PDPs) must therefore attend to all the components of innovation, including intellectual property, in the quest to ensure global access.[4]

The emergence of PDPs over the past decade has provided a unique mechanism, a hybrid public/private approach, by which to generate new products for the neglected diseases of poverty. PDPs employ a variety of strategies to achieve goals (for example, creating new technologies and ensuring that the developed technology is available and affordable to as many beneficiaries as possible in the developing world). The most basic challenge is to provide access to needed technologies and pay close attention to how the technology is to be distributed or marketed, while simultaneously offering appropriate incentives to private sector partners to encourage the commitment of research, development, and manufacturing resources. To do this, PDPs are both charting new territory and employing management models that borrow frequently from the private sector. Moreover, in some cases PDPs have reinvented R&D approaches for preventing and treating human diseases. Unlike traditional R&D agreements, PDPs must make deals that extend well beyond the scope of traditional commercial agreements, stipulating access conditions to ensure that the product reaches the target population. These terms and conditions frequently focus on the strategic use of intellectual property and often have to address such issues as market segmentation, pricing, and distribution.

The experiences of PDPs have shown that several factors are driving some companies to work collaboratively and to share disease-related intellectual property. These factors include corporate social responsibility and strategic considerations, such as positioning in emerging markets. An additional incentive is the potential that R&D projects with PDPs may have relevance for commercial compounds. For example, MMV carries out joint studies on malaria tetracycline resistance with industrial partners, which benefits their commercial anti-bacterial research.

PDPs are an increasing and innovative group of organizations. The diverse experiences of PDPs can help inform the makeup and negotiation of R&D partnerships and lead to better agreements dealing with the various forms of IP. Several PDPs are reaching a new mature phase, with products in clinical development for poverty-related diseases. These PDPs have designed workable solutions to ensure access and affordability, from planning production that will meet the size of demand, to addressing issues of end-user acceptability. PDPs are pioneering a new form of social contract to promote the development of health products where commercial incentive is lacking.

To promote and facilitate discussion among those who have embarked on or are developing plans for PDPs, the Centre for the Management of Intellectual Property in Health Research and Development (MIHR) and the Aeras Global TB Vaccine Foundation, in partnership with the Bill and Melinda Gates Foundation, convened a meeting titled Ensuring Global Access through Effective Management of Intellectual Property in 2006.[5] It built on a similar joint meeting held

in 2004, also involving around 50 participants including senior management, legal counsel, program officers, and business development professionals from institutions and organizations involved with PDPs.[6]

This chapter summarizes presentations made at the meeting by representative PDPs. Their stories illustrate the diversity of approaches used in making R&D agreements and managing intellectual property in the context of global health. The structure of these agreements defines and is influenced by the relationships among the partners. As Oehler noted:

By the nature of their business model, the commercial interests of private sector companies are, on the whole, oriented toward maximizing profitability. It is not justified to expect that private sector business will automatically ensure best services to the public sector and focus the generation and use of intellectual property toward maximized public-sector benefits.

To prepare for a situation where the original targets of a license agreement are delayed or are not achieved, and to avoid the situation where projected public-sector benefits are delayed or are not realized, it is good practice to establish contractual milestones that regulate target achievement under the license and to set incentives to keep to timelines and performance accordingly. This allows licensor and licensee(s) to focus resources on their efforts to perform as was agreed upon in the first place.[7]

2. PDPS IN ACTION

2.1 *Collaborative research with centralized IP management: DNDi*

Nicoletta Dentico noted that several PDPs focus on creating R&D partnerships to achieve outcomes that would otherwise be impossible. For example, in 2003, seven organizations from around the world joined forces to establish the Drugs for Neglected Diseases initiative (DNDi).[8] Among the seven were five public-sector institutions, one humanitarian organization, and one international research organization.

DNDi was created in response to the fact that of all the new drugs developed over the past 30 years, drugs for tropical diseases and TB account for only 1.3%. The organization itself does not conduct research and scientific work to develop drugs. Instead, it capitalizes on existing, fragmented R&D capacity, especially in the developing world, and complements it with additional expertise as needed. According to Dentico, the DNDi policy advisor, this integrative approach helps cut costs.

The group builds its portfolio by identifying medical needs and R&D opportunities and then seeking letters of interest to conduct R&D projects. Current projects by academic and industrial laboratories are focused on identifying new drug candidates for tropical diseases, such as trypanosomiasis, which afflicts over 66 million people in 36 countries of Sub-Saharan Africa. Other projects involve developing products that simplify and reduce the length of malaria treatments. Participating partners provide funding, pharmaceutical development, in vitro and molecular studies, development of analytical models, animal toxicity testing, and clinical trials, all under DNDi coordination and management. This collaborative mode of operation blends centralized management, which gives a clear project-specific focus, and decentralized operations, which mimic modern drug companies.

DNDi has also built regional networks of scientists actively involved in the research of new drugs for neglected diseases in Asia, Africa, and Latin America. These regional networks, coordinated by DNDi regional liaison officers, are vital to the success of DNDi. They are able to collect data on available regional expertise, capacity, and patients' needs, and they actively advocate for DNDi by encouraging scientists to submit proposals to DNDi.

DNDi negotiates intellectual property and knowledge dissemination agreements to obtain the best possible conditions for patients and to ensure that the fruits of DNDi-sponsored research will be readily available and affordable in developing countries. Exclusive rights, titles, and interest in the results of a given research project are retained by DNDi, including but not limited to any resulting patents on any inventions. DNDi decides on the best way to make the results of a

research project available to the public, including by putting the results in the public domain with no limitations.

In addition, DNDi may choose a number of IP management options: (1) apply for patent protection to protect some or all of the outputs of a research project, (2) keep such outputs confidential, or (3) take any other measures that would promote DNDi's mission (such as publicly disclosing the results). To ensure that DNDi can make full use of the results of a research project, DNDi asks partners to grant a nonexclusive, worldwide, royalty-free, irrevocable license to use any background IP rights that may be needed to develop and commercialize a compound developed during the course of a research project.

According to the experience of DNDi, forging agreements with North American universities is often a lengthy process: the average negotiating time with academic entities in the United States and Canada is eight months, whereas the average negotiating time in Europe is four months. Dentico added that PDPs could provide useful collaborative R&D models to borrow from and to create precedents for improving the current R&D environment. This is especially the case for filling needs not adequately addressed by government investment, which often focuses on the earliest stages of research. Unlike some other PDPs, DNDi focuses much of its efforts at the public sector level. In addition, DNDi wages public information campaigns that urge citizens to advocate governments to fund research on diseases of the poor.

2.2 *Bridging academe and industry through social entrepreneurship: iOWH*

Often characterized as the first nonprofit pharmaceutical company in the United States, the Institute for OneWorld Health (iOWH) is another example of a PDP focused on finding new drug candidates for the developing world. Katherine Woo, director of scientific affairs at iOWH, pointed out that the focus of the company is to remove the profit element from the business plan and to build a global organization with core competencies in R&D and regulatory approval for new drugs. A defining feature of iOWH is its social entrepreneurial component, which aims to deliver medicines to the world's neediest populations.

According to Katherine Woo, the strategy is to assemble an experienced team of pharmaceutical scientists to identify the most promising drug and vaccine candidates—often, the most promising drug candidates are those that have been discarded for lack of a viable market. Once such candidates are identified, iOWH focuses on developing them into safe, effective, and affordable medicines. The group then partners with companies, nonprofit hospitals, and organizations in the developing world to complete the requisite animal studies, conduct clinical trials, secure quality manufacturing in disease endemic countries, obtain regulatory approval, and distribute newly approved therapies.

The group's strategy, according to Woo, is based on the assumption that pharmaceutical R&D to create the new medicines for the developing world need not involve huge costs. By partnering and collaborating with industry and researchers, securing donated intellectual property, and relying on and using the scientific and manufacturing capacity of the developing world, needed vaccines and drugs can be delivered affordably and effectively. The PDP's goal is to provide the bridge between novel bench science and its conversion into applications for the developing world. For example, industrial scientists are brought together to assist university scientists on late-stage processes, such as high-throughput screening and lead optimization of potential new drugs.

Carrying basic scientific research forward through product development requires the participation of many groups; however, one partner ultimately must take responsibility and be held accountable if new drug development is to be successful. In many cases iOWH serves as that global development partner. It takes responsibility for markets in the least developed countries (dual market opportunities) and obtains resources from private foundations and governments to fund the development costs of taking a new drug through to market in the developing world. In addition, iOWH provides international regulatory expertise to increase the number of countries in which important new drugs are marketed.

The company interprets global access as affordable prices, a sustainable supply, and engaged distributors. It directly controls pricing as much as possible and attempts to maintain maximum flexibility to engage downstream partners (for example, by offering royalty-free licenses). Negotiations on geographic coverage for marketing, public sector price and exclusivity considerations can be complex and protracted.

As a nonprofit corporation, OneWorld Health provides a tax deduction for the projected future value of donated intellectual property. However, iOWH seeks exclusive licensing to protect investment by philanthropy. Woo emphasized that iOWH tries to avoid being surprised in its IP management strategy and that they are always on the lookout for intellectual property that has the potential to discourage important research in developing countries. When the IP requirements of a partner become too burdensome or onerous, the group sometimes walks away from the deal and searches for another partner.

2.3 *Managing intellectual property in a research consortium: IAVI*

Some PDPs serve as enabling bodies to create incentive systems, modes of operation, and negotiators for IP management. The International AIDS Vaccine Initiative (IAVI) focuses on spurring R&D for the development of safe, effective, and accessible preventive AIDS vaccines for use throughout the world. Labeeb Abboud observed that, in addition, IAVI is involved in advocacy work, seeking to secure and sustain global, national, and local community involvement and commitment for the development of an AIDS vaccine. Efforts focus on the developing world, where the epidemic is most severe.

IAVI is supporting research into several key, unresolved questions of vaccine development. Among other projects and lines of investigation, their effort involves a consortium of academic and industrial research laboratories focusing on HIV-neutralizing antibodies, mechanisms of protection, and vector design. The consortium currently has 16 members located in the United States and Europe. IAVI negotiates the joint work plan and provides a governance structure. The members of the research consortium have agreed to common provisions relating to IP management and ownership, including access provisions. IAVI is provided with license rights to program intellectual property, and certain background intellectual property, and is responsible for diligently pursuing further development. Future licensing revenues are to be shared among all members, with the expectation that no royalties will be received from developing country sales. Key to the effective functioning of the consortium are the close working relationships among its members.

IAVI also has had several vaccine development programs; it is currently conducting human clinical trials of three vaccine candidates in the United States, Europe, Africa, and India. Although consistency in IP management is sought, flexibility in the approach to IP ownership, management, and licensing is also important. Ownership may be determined by inventorship, by ownership of background intellectual property, or by funding. License rights to program intellectual property may be exclusive or nonexclusive, and they may be worldwide or restricted to certain geographic sectors. With respect to partnerships in which IAVI's partners control the intellectual property or license rights, and thus are responsible for manufacturing and distributing a future vaccine, IAVI's contracts require that the partners make access commitments for the developing world (relating to price, quantity, and availability) and provide IAVI with remedies, such as march-in rights, to ensure that products developed through the consortium are made available to people in need.

There are a number of challenges that arise in the contracting process, as well as in the management of the ongoing relationships with partners. Some of the greatest challenges are in the IP area, with regard to due diligence, management (when to file and where), meeting the requirements of donors (including audits), and establishing termination rights.

2.4 *Tailoring IP provisions for each agreement: Aeras Foundation*

The Aeras Global TB Vaccine Foundation, founded in 1997, is an international nonprofit PDP working toward developing a vaccine against TB,

both at Aeras facilities and in collaboration with academic/industrial partners. Rita Khanna, the foundation's legal counsel, explained that Aeras actively pursues and helps fund joint-development activities with leading TB vaccine developers around the world. It also develops candidate vaccines in its own laboratory. Aeras's partners with other groups in order to develop vaccine candidates and field sites for clinical development and to ensure vaccine supply. Aeras' partners include companies in nine countries, academic laboratories in eight countries, and five foundation or government partners. It is the goal of Aeras to develop, test, characterize, license, manufacture, and distribute at least one new TB vaccine within 10 years.

Aeras takes promising research and early-development candidates through preclinical regulatory requirements; clinical phase one, two, and three studies; process development; manufacturing; and release. The overarching scientific strategy is to improve the current, widely used bacille Calmette-Guérin (BCG) vaccine—which has limited efficacy—and boost the current BCG vaccine with either a recombinant TB protein plus adjuvant or a recombinant viral vector making TB antigens. Prime-boost regimens of this sort have proven to be the most powerful inducers of immune responses and protection against TB in animal models.

The focus of Aeras's IP management strategy, according to Khanna, is to ensure global access to any resulting vaccine. Aeras has executed numerous research collaborations, licensing, and other agreements with commercial and academic partners. In one joint development collaboration, the partner owns the background intellectual property, while the ownership of new intellectual property is determined by inventorship. Aeras has a royalty-free, sublicensable exclusive license to distribute and sell in developing countries and public markets in emerging economy countries (EECs), and the partner has a royalty-free, sublicensable exclusive license to commercialize in developed countries and private markets in EECs. The partner has the first right to negotiate—and right of first refusal—to an exclusive manufacturing contract to supply Aeras with vaccine for sale in developing countries and public markets in EECs. If the partner is not able to meet the demand of vaccine for distribution by Aeras, then the partner must transfer the rights to Aeras or to a mutually acceptable third party. Should the partner breach the contract, Aeras would negotiate a license to continue commercialization for developing countries and EECs.

A second type of agreement has many of the same provisions, except Aeras and the partner have a royalty-free, coexclusive license to distribute and sell in developing countries with a right to grant one sublicense. In this scenario, the collaborator has the exclusive right to commercialize in developed countries and EECs. In addition, Aeras has a royalty-free license for EECs if the partner has not pursued regulatory approval within three years of regulatory approval in an industrialized country. The partner has manufacturing rights for the first five years only. Should the partner breach this contract, Aeras has a nonexclusive license to continue development in the licensed territories or the right to select an alternative manufacturer.

In similar agreements, Aeras has negotiated terms in which the collaborator may use a "reasonable commercial effort" to manufacture and supply the product. In addition, the collaborator may provide the vaccine at two-tier differential pricing in public and private markets. In this scenario, no IP rights are granted to Aeras.

Other agreements focus on license rights: Aeras has a nonexclusive license in EECs in one case and an exclusive, worldwide license in another case. In these types of agreements, Aeras owns improvements and pays license fees, patent prosecution costs (past and future), minimum annual royalties, milestone payments, and royalty on net sales. These agreements typically include royalty-stacking terms.

In a clinical trial agreement, Aeras retains rights in intellectual property relating to clinical trials, although there is joint ownership of intellectual property resulting from epidemiological studies. In a sponsored-research agreement, Aeras provides funding for the research and has an exclusive, first right to negotiate an exclusive or nonexclusive, royalty-bearing license to make, use, and sell any patentable inventions conceived

and reduced to practice during the term of and in the performance of the research supported by Aeras. In another sponsored-research agreement, Aeras owns all rights, title, and interest in and to any intellectual property, material, data, and records derived from performance of research supported by Aeras.

Many of these agreements contain other key provisions related to confidentiality, publishing rights, patent enforcement and infringement, indemnification, liability and insurance, law and jurisdiction, dispute resolution and arbitration, and termination.

2.5 *Ensuring access to new drugs: from aspiration to operation at MMV*

Richard Wilder noted that while many PDPs focus on early-stage efforts to discover and deliver new drugs for neglected diseases, few have reached the point of delivery. Indeed, planning for the access and delivery of new drugs in disease-endemic countries cannot be accomplished by one PDP working alone.

The efforts of Medicines for Malaria Venture (MMV) are focused on both delivery and R&D. Formed in 1999, MMV is a nonprofit organization created to discover, develop, and deliver new antimalarial drugs through effective public–private partnerships. MMV brings together global public health organizations, the pharmaceutical industry, government ministries, research institutions, and foundations to combine their expertise and resources to ensure the needed research, development, and release of antimalarial drugs.

Currently, MMV is managing more than 20 projects that are in various stages of drug R&D, and several in Phase Three clinical trials, with reports that good progress is being made. The group's goal is to register at least one new antimalarial drug before 2010 and to maintain a sustainable pipeline of antimalarials that can meet the needs of the more than 2.4 billion people at risk.

These goals are bolstered by MMV's groundbreaking collaboration with nearly 40 public and private institutions around the world. In particular, MMV entered into discussions with pharmaceutical companies conducting anticancer therapy research that led to the development of compounds that are highly active against the malaria parasite.

Because much of MMV's focus is on later-stage issues, it already is discussing with collaborators provisions for pricing agreements, negotiating third-party rights, and ensuring that sufficient quantities of the drug are available once developed. Provisions for handoff are discussed and negotiated well in advance. All parties must understand the goals, the need for speed, and a clear view of the regulatory pathway in each country where drugs are being tested. MMV negotiates time limits for late-stage clinical trials and filings. Products are registered and launched immediately following regulatory approval. In addition, deals with collaborators include requirements for quality assurance.

MMV manages the ownership and licensing of intellectual property so that the partners' interests are reflected in the terms of agreements. Depending on the situation, MMV might own the intellectual property outright, retain licenses to the intellectual property, or place conditions in its agreements that, if not met, will transfer IP rights back to MMV. Sometimes MMV's ownership of IP rights is unnecessary because the group is working with a company to both discover and develop a promising compound as an antimalarial. In those cases, the company might retain ownership of the IP rights for use in meeting their obligations to MMV to develop and bring an antimalarial to market.

MMV's agreements specify the conditions that have to be met, including price specifications and access requirements (for example, access milestones). The experience of MMV suggests that setting access milestones should not be done too late in the process, when time pressures are heightened. Pricing agreements, moreover, are particularly challenging because of the division of markets in many countries where MMV is working. And difficulties can arise if the price issues are driven too far in advance. An advance commitment to a set price ceiling can, for example, deter investment. If a partner company cannot or will not meet the conditions of the agreement, MMV requires that IP rights be returned so it can seek another partner. However, the focus of deals

is not on IP rights per se, but rather on the ability of MMV to ensure that new antimalarial drugs under development are brought to market and made affordable and accessible to those who need them in the developing world. From MMV's perspective, IP rights are merely a tool to help bring partners together toward a common goal.

2.6 *Securing candidate products through creative licensing: IPM*

The International Partnership for Microbicides (IPM) is a nonprofit PDP established in 2002 to prevent HIV transmission by accelerating the development and availability of safe and effective microbicides for use by women in developing countries. Paul Model explained that IPM's basic strategy involves the licensing of active compounds from commercial pharmaceutical companies for development as microbicides. IPM already has announced compound licenses with Johnson & Johnson/Tibotec, Merck, and Bristol Myers-Squibb. IPM has found that larger pharmaceutical companies are more likely to grant licenses on a no profit/no loss basis.

IPM promotes the rapid development and delivery of safe and effective microbicide products by pioneering best-practices approaches to:

- screen compounds and design optimal formulations
- develop clinical trial sites and conduct clinical trials
- identify appropriate regulatory pathways for microbicide products
- establish manufacturing and distribution capacity to ensure rapid access to a microbicide as soon as it becomes available

IPM also funds, co-funds, or leverages resources to support the drug development projects of other entities. In some cases, however, the most efficient approach is for IPM to take the lead in developing, testing, and conducting clinical trials of promising microbicide compounds. In this role, IPM is the technology developer and receives a nonexclusive license from the owner of the compound that is royalty free and permits distribution on an affordable basis in resource-poor countries. Rules and procedures are, however, imposed on access to the compound for research purposes. Importantly, the compounds in development remain proprietary. Thus, a grant-back license to the owner of a compound typically is required for modifications to the compound. Grant-back licenses of products or formulations are subject to negotiation.

According to Model, one of the more important aspects of negotiations involves defining what constitutes a resource-poor country. In his experience, each partner has its own list of countries; there is often disagreement over whether certain countries, such as China, India, and Brazil, qualify as resource-poor. However, so far IPM and its partners have succeeded in reaching agreement on this issue. In some cases, IPM has obtained worldwide rights, recognizing that compounds are still proprietary and ensuring that products will be made available on an "affordable basis."

Other important issues involve territory and access. Some granting organizations are particularly concerned about access to results of funded research. IPM has encountered complex "public sector pricing regimes" in grant agreements that are similar to those proposed to several other organizations. These may present inconsistencies with the structure of the licenses that IPM has been able to negotiate with commercial pharmaceutical companies. IPM strives in all cases to reach agreement on affordable-basis criteria in all agreements. These criteria include no compensation for intellectual property or development costs, manufacture at lowest reasonable cost consistent with quality, and recognition that IPM's rights under its licenses are limited. Although some collaborators are initially resistant to these or other terms, peer pressure and the desire to do the right thing are frequently the motivating factors in closing a deal.

2.7 *Deal making with a marketed product: TB Alliance*

Two billion people—one-third of the global population—are infected with *Mycobacterium tuberculosis*. More than eight million people develop active diseases every year and two million people die from the disease. Existing drugs are 40 years old and impose a daily regimen that is long and

cumbersome, which slows the control of the disease and promotes the rise of drug-resistance. In addition, TB/HIV co-infections are fueling each other, and multidrug-resistant TB (MDR-TB) and extremely drug resistant TB (XDR-TB) cases are on the rise.

Gerald Siuta explained that the Global Alliance for TB Drug Development (TB Alliance) is a not-for-profit, product-development partnership that aims to accelerate the discovery and/or development of affordable, new TB drugs. It is hoped that such drugs will shorten treatment and be easier to take, be more effective against drug-resistant strains, be appropriate for patients with HIV-TB co-infection, and be capable of improving the treatment of latent infection.

In its first five years, the TB Alliance has built the most robust TB drug pipeline in history, helping to fill a gap left by the private sector. Any new drug regimen must be more than just highly effective and easy to use; it must also be universally affordable, adopted, and accessible. According to Siuta, this "AAA" goal guides all decisions on project selection and development, as well as concurrent work to influence the policy and regulatory environments to foster appropriate pricing in developing countries, ensure that new drugs are incorporated into existing treatment programs, and facilitate procurement and distribution to those patients who most need the drugs.

One of two TB Alliance's projects now in the clinical phase is the testing of moxifloxacin for the treatment of TB. Moxifloxacin is a fluroquinolone antibiotic already approved in 104 countries to treat respiratory and skin infections. It is novel in that it kills mycobacterium TB through DNA inhibition. Moxifloxacin has been shown to reduce treatment time by two months when substituted for isoniazid. Moreover, it is safe when used in combination with antiretrovirals.

In October 2005, the TB Alliance and Bayer Healthcare announced a partnership to coordinate a global clinical trial program to study the potential of moxifloxacin to shorten the standard six-month treatment of TB. Clinical trials will assess the efficacy and safety of moxifloxacin as a front-line agent for the treatment of TB. If successful, the partnership will register moxifloxacin for a TB indication. Both parties are committed to making the product affordable and accessible to patients in the developing world. Nearly 2,500 TB patients are being enrolled in trials in Brazil, Canada, South Africa, Spain, Tanzania, Uganda, the United States, and Zambia.

Bayer has committed to donating moxifloxacin to each clinical trial site, covering the costs of regulatory filing, and providing moxifloxacin at an affordable price for patients with TB in the developing world. The TB Alliance has committed to coordinate and help cover the costs of the clinical trials, ensure coordination of information and results for registration goals, and leverage substantial support from the U.S. Centers for Disease Control and Prevention, the Orphan Products Development Center of the U.S. Food and Drug Administration, and the European and Developing Countries Clinical Trials Partnership.

A crucial aspect of the deal was ensuring that Bayer's market for moxifloxacin was protected. At the same time, if a TB indication is approved, there is a potential for dual markets in which there would be separate pricing and distribution plans.

2.8 *A focus on diagnostics: FIND*

Herbert Clemens discussed The Foundation for Innovative New Diagnostics (FIND), launched in 2003 at the World Health Assembly in Geneva. FIND is a nonprofit organization based in Switzerland and dedicated to the development of rapid, accurate, and affordable diagnostic tests for poverty-related diseases in the developing world.

FIND aims to provide a bridge that can effectively link academic research and the diagnostic industry to the specific needs of developing countries. The agency provides this bridge by leveraging the strengths of its diverse partners to develop technological platforms for diagnosing poverty-related diseases in the public, as well as the private, health sector. Working in close collaboration with the Special Programme for Research and Training in Tropical Diseases (TDR) of the United Nations Children's Fund, the United Nations Development Program (UNDP), the

World Bank and the World Health Organization (WHO), the diagnostics industry, and other organizations, the Foundation develops and validates affordable, novel diagnostic tests for diseases in high-burden countries. It is leveraging new technologies that have revolutionized the simplicity, speed, and accuracy of diagnostic tools for identifying diseases in the developed world.

FIND conducts its business essentially as a spinout venture and has project portfolios in the areas of malaria, TB, and sleeping sickness. Although it is involved in project management at all levels—financial, administration, strategic planning, business development, communications, information technology, and legal services—FIND focuses on the middle spectrum of product development. FIND leverages its investments to secure affordable pricing in developing countries, thus helping to ensure equitable access to diagnostic products for those most in need of them.

Clemens noted that although FIND has IP expectations for each project, there is a high degree of good faith among collaborators. IP ownership generally rests with the partner. At the end of a project, FIND negotiates with the collaborator on how to dispose of the intellectual property.

One of the most challenging issues is dealing with market segmentation. Of the 193 countries in the world, only 25% are developed, and many have dual markets, so FIND must arrive at pricing agreements that satisfy both the market requirements of a sponsor (unit product cost plus mark up) and FIND's own access requirements

2.9 *Biotechnology investment in global health: BVGH*

Christopher Earl observed that biotechnology companies lead the world in developing new health care products, often for "orphan diseases," conditions for which the development of drugs in not commercially viable or that are rare. However, few companies have focused on developing treatments for neglected diseases. While many biotechnology industry leaders are dedicated to contributing to advances in global health, their companies often perceive market, financial, and information barriers that limit their involvement.

BIO Ventures for Global Health (BVGH) combines expertise in industry, in investing, and in policy to bridge biotechnology and global health. It operates on the assumption that because technology platforms are already built and "*money is already sunk*," there is good reason to take advantage of the existing infrastructure for creating medicine for diseases of the developing world.

BVGH was spun out of the Biotechnology Industry Organization (BIO) and is supported by the Bill and Melinda Gates Foundation and The Rockefeller Foundation, as well as by leading biotechnology companies. Earl noted that with more than 4,000 companies and 270 approved products on the market, the biotechnology industry has created an extraordinarily diverse set of high-technology platforms for drug discovery, and thus is well situated to take on the challenges of global health.

BVGH's approach is market based: it seeks to create or facilitate economic incentives and market mechanisms. Its approaches include: (1) identifying targets for the development of new drugs, vaccines, and diagnostics; (2) identifying market opportunities for neglected diseases through a series of disease-specific business cases; (3) working with companies to build global health strategies that optimally employ their core capabilities; and (4) expanding access to information and resources, providing opportunities to exchange information, facilitating new partnerships, and securing financing for the most persuasive projects.

According to Earl, the biotechnology industry is made up of three tiers. Top-tier companies are the largest and "*act like pharmaceutical companies*." These companies are in the process of building social responsibility models within their organizations. Second-tier companies are institutionally backed. They are "*preprofitable*," their investors are "*tough,*" and company strategies are still focused very much on opportunity costs and avoiding potential loss of focus. The third tier consist of very small companies, essentially "*mom and pop*" operations. The second tier companies are often the best targets for BVGH efforts

because they have the infrastructure in place, have financial backing, and yet are not committed to a binding, long-term R&D plan. Moreover, if a PDP already has pathways for production or manufacturing, it reduces the opportunity costs for such companies in that they can transfer their technology directly to the effort without high costs.

In brokering deals between PDPs and biotechnology companies, the innovation should be in the product, not in the deal. Anytime one can use existing agreements as models for moving forward, time and costs will be minimized, both of which are at a premium for PDPs and midsize biotechnology companies.

2.10 *An agricultural model for cooperative IP management: PIPRA*

The Public Intellectual Property Resource for Agriculture (PIPRA) is not a PDP, but rather an initiative by universities, foundations, and nonprofit research institutions to make agricultural technologies more easily available for the development and distribution of subsistence crops for humanitarian purposes in the developing world and for specialty crops in the developed world.

Alan Bennett explained that although the IP stakes are low in agriculture, the social and human health stakes are quite high. Traditionally, discoveries in public research institutions and agricultural universities were seen as "*public goods*" that flowed directly down the chain of public institutions to farmers and businesses. This system formed the basis for crop improvements and a robust seed industry in developed countries while significantly increasing food production in several developing countries.

In the past few decades, however, changes in U.S. patent law and university technology transfer programs have resulted in an increasing use of the patent system to protect agricultural innovations. In many cases, dominant patents held by the public sector were licensed for private use. Companies then adopted and often improved discoveries from public sector institutions and turned them into crop varieties for commercial markets. However, because of the many public institutions conducting agricultural research, the overall portfolio of public sector technologies is highly fragmented across multiple institutions and technology categories. Information about existing technologies and where rights are held is difficult to find. In addition, more intellectual property has been licensed to the private sector, sometimes under terms that are confidential and often that provide exclusive rights to the licensee. Since applied research and crop genetic improvement is a derivative process based on preexisting plant material, each incremental improvement that involves biotechnology can bring with it a number of intellectual property and germplasm constraints, which accumulate in the plant material. As a result, it has become more difficult for public sector researchers to access technologies to fulfill their missions, especially with regard to developing sustainable agriculture for the developing world.

The development of vitamin A-enhanced rice, or "Golden Rice," illustrates the consequences of the complex IP ownership of agricultural biotechnology. Golden Rice provides dietary vitamin A when consumed. Thus, it offers direct health benefits to millions of poor children in developing countries, where vitamin-A deficiency causes 500,000 cases of blindness each year, and is a contributing factor in over two million premature deaths each year. However, when the time came to prepare this product, many of the techniques used by the researchers were patented in some countries, and some of the materials had been used informally, or under legal agreements that restricted further dissemination. There were 70 proprietary technologies involved, including 40 issued patents in the United States and more than a dozen material transfer agreements (MTAs). Although these issues have now been largely resolved through the cooperation of the private and public sector, much effort was expended to overcome these barriers.

As a result of this and other cases, PIPRA was formed to help public sector agricultural-research institutions achieve their public missions by ensuring access to the intellectual property they need to develop and distribute improved crops. Two PIPRA programs of relevance are focused on IP best practices and management. One program

is exploring and clarifying the implications of public sector IP licensing practices and is seeking a series of best practices that will encourage the commercial development of publicly funded research innovations. At the same time, PIPRA will also retain rights that public research institutions need to fulfill their mission of research for the broader public benefit.

Another PIPRA program involves building an IP database. Currently, the database contains over 6,600 patents and patent applications from 39 different countries. Using the database, these patents are searchable with respect to various parameters, including licensing status. The data represents the agricultural portfolios of 27 participating universities and nonprofit research institutions. The goal of the database is to inform public sector researchers about their freedom to operate (that is, clear all IP barriers to bringing a new product to market). The software also finds ways to invalidate patents and minimize the chances of patent blocking. Use of the database and PIPRA's analytical services are free for academic research and humanitarian purposes.

3. KEY LESSONS

Many different models exist for identifying candidate drugs, vaccines, and technologies, from owning inventions to finding new uses or markets for already-marketed products or abandoned product lines. After patents have been issued, the IP issues and liability concerns become simpler to manage, since there will be an increasing amount of safety data available. Partners owning the intellectual property are able to provide the background technology and expertise, setting conditions for licensing and access.

There is no single business model that PDPs ought to pursue. PDPs vary from virtual organizations that contract all aspects of product development, to universities and firms, to PDPs that have developed considerable international capacities and expertise in product management and regulatory affairs. Regardless of the type, all PDPs negotiate diverse ranges of agreements, including, sponsored-research contracts, know-how and patent licenses, and distributorship agreements.

Although their business models vary, PDPs employ a common set of strategies to manage intellectual property for global health outcomes, usefully summarized by Antony Taubman of the World Intellectual Property Organization. These include:

- defining a discrete territorial market (separating industrialized markets from developing countries, or focusing on target markets), allowing investments and earnings from Organisation for Economic Co-operation and Development markets to subsidize product availability in developing countries
- establishing distinct structures for public sector marketing, social marketing, and private markets (for example, more open licensing for the public sector balanced by exclusivity over lucrative markets)
- determining field of use in a manner that enables the covered technology or product to extend to indications for conditions of prevalence in industrialized countries, where feasible, as an investment incentive
- establishing royalty rates in a manner that benefits the party requiring the greatest incentive
- providing for access to the developed technology in the event that the research/industry partner abandons the project or does not service a particular sector, including background and foreground intellectual property, product development know-how, and regulatory approval data

If the industrial partner bears some of the risk, because of early-stage involvement either through investment or conduct of R&D, then IP issues, such as agreements about royalties, licenses, and access, must be resolved early on. These issues can be quite complex. The different levels and forms of contribution by the partner will influence the extent of and flexibility of the terms. If multiple partners are involved, each with background intellectual property and expectations for foreground intellectual property, then royalty-stacking provisions may be required.

3.1 *Preparing for access*

As PDPs plan for access, they face a series of practical and conceptual challenges to ensure supply, an affordable price, and effective delivery once the product is successfully developed. An analysis prepared for WHO's Commission on Intellectual Property Rights, Innovation and Public Health by Jon Merz, indicates that many PDP R&D contracts defer downstream issues related to manufacturing and distribution to future resolution. Operational challenges face PDPs with regard to pricing to the public sector, market segmentation, market sizing, ensuring the lowest sustainable cost of production, and quality control, as well post-launch issues, such as pharmacovigilance and product liability.

Specifying requirements and strategies for access early on is critical so that unsurmountable hurdles or costly delays are not encountered once the product is developed. Indeed, experience demonstrates that even where certain products have been developed for distribution in developing countries, uptake has been sluggish or stalled due to a variety of downstream constraints. This has been the case, for example, with the combination antimalarial Coartem; praziquantel, for the treatment of schistosomiasis; and the slow uptake of hepatitis B vaccines. Some PDPs, especially those that face inadequate delivery systems in target countries (regarding deployment of microbicides or HIV vaccines, for example), have identified preparation for access as a core aspect of their mission and have begun to document their needs. Moreover, the GAVI Accelerated Development and Introduction Plans are forging approaches for the phased introduction of selected vaccines.[9] In some cases, PDPs also may be able to work with *access* public–private partnerships in fields where they exist (e.g., Roll Back Malaria Partnership), especially with regard to pricing and financing mechanisms and delivery networks in target countries.

An important tool in intellectual property management is the detailed development of contractual milestones in licensing intellectual property from public to private sector, including provisions for performance review and modifications, when required. Key milestones include pricing to the public sector, territory and exclusivity; regulatory work and time to market; royalties and terms; and termination of the licensing agreement.

3.2 *Pricing issues*

A key consideration in access negotiations is target pricing. PDPs typically require the product to be made available at affordable or reasonable pricing, which may lead to complex negotiations about how to calculate price, or consideration of available price discriminate models. Price setting requires both parties to know in advance the technical details of production, marketing, and distributions costs. A clear framework to compute manufacturing cost is required. Since many PDPs enter negotiations based on early-stage discoveries, stipulating price in a contractual arrangement could be a risky or impractical proposition. In most instances, the cost of the final product is the cost of production plus a reasonably negotiated mark-up. Assessments on what constitutes an affordable price are complex, since they take into account the epidemiology of the disease, purchasing power of those affected, and government financing schemes, among other factors. In comparison to drugs, where one can project costs once a compound is identified, pricing is more difficult with vaccines because one does not know in advance what the acceptable price will be or what a government might support. There was general agreement that pricing done too far in advance can deter industry partners and discourage extended R&D commitments. Approaches to calculating price are a priority topic for focused exchange among PDPs and relevant experts.

3.3 *Market segmentation*

Market segmentation has emerged as a common issue in negotiation. Although there are common sources for differentiating countries (for example, World Bank income data), challenges emerge with the division of rights in so-called mixed-payer markets, such as Brazil and India. As more agreements are pursued, it would be useful to generate descriptive case studies on price tiering and its effectiveness at segmenting domestic

markets. A correlative need is to prevent arbitrage or leakage between public and private markets.

3.4 *Production and capacity issues*

Production also must be addressed. PDPs pose a new business model with new challenges, (for example, convincing a party to build a factory with uptake, rights, and options for manufacturing and operations that are uncertain). Identifying existing facilities is a strength for some PDPs. Those working in vaccines, however, have a greater challenge in that for regulatory reasons, they must find a purpose-built factory for every vaccine. While excess capacity can typically be absorbed for drug manufacturing plants, the same is therefore not the case for vaccines. Thus, the price of a vaccine is linked to the cost of production and investment in the manufacturing plant.

Another critical issue is projecting and assuring capacity commitments as products approach the large-scale processing stage. Some therefore suggest that in some cases there should be publicly dedicated capacity for manufacturing and that PDPs should enter into deals with that expectation in mind.

3.5 *Early-stage licensing*

In negotiations with universities, several PDPs note challenges with in-licensing the needed technologies from academic institutions. Universities may overvalue inventions or lack flexibility. However, through the efforts of organizations such as MIHR and PIPRA, many universities are becoming increasingly able to use IP tools to promote access in developing countries, such as through the use of humanitarian licensing provisions.

There are several constructive actions that could assist the PDPs, including the establishment of inventories of IP rights held and a survey of the licensing status in key global health fields. A prototype database is being developed at the U.S. National Institutes of Health (NIH), based on the U.S. Federal Interagency Edison database of invention reports. At the institutional level, there is growing interest among technology transfer offices to operate against performance expectations aligned with both economic and social goals. AUTM is considering new initiatives in performance metrics, which potentially could facilitate academic licensing to PDPs, if measurements incorporate global health or global access considerations.

In some instances, negotiations with small biotechnology firms are comparably difficult. Such firms are sometimes concerned that sharing platform technologies for use in the development of noncommercial products may weaken commercial positions. The types of outreach initiatives undertaken with universities may equally benefit small biotechnology companies (for example, through dissemination of case studies). A key challenge is to demonstrate creditable demand to encourage risk taking by corporate partners. In several areas (HIV, pneumococcal, and rotavirus vaccines), useful modeling work is being pursued to assess demand and its implications for financing mechanisms.

3.6 *Negotiating the IP landscape*

PDPs practice due diligence and, where needed, engage in IP mapping exercises to ensure freedom to operate. IP assembly issues are becoming more challenging, due to the increasing need for proprietary tools. This is especially the case for broad umbrella or vaccine component patents, where a variety of technologies may be required to express or purify an antigen, bolster immunity, or devise a delivery system. Related problems include royalty stacking and lack of ownership of intellectual property to cross license.

Responses to patent thickets include license mapping and exploring creative licensing schemes. There is an emerging range of IP management tools that can be applied, depending on the particular needs of the scientific challenge. However, more systematic efforts are needed to identify where and when current or emerging IP management strategies might best be considered and to facilitate their application. The challenge may be to identify the specific technology platforms around where public and private sector product development interests strongly coincide. It is also important to identify the key institutions to bring together to discuss such a consortium-based approach. Negotiating the patent landscape

and access to research tools is a general challenge for the scientific community. However, creative models in the health sciences may find the most fertile ground in the context of global health products, since they represent noncommercial, or "low margin," R&D.

3.7 *Systemic challenges*

The workshop emphasized the broader systemic needs of the PDPs, including distribution challenges within countries with poor infrastructures. Reducing the time gap between development and implementation also will require the continued development of an international clinical trials system that engages local investigators, communities, ethical review committees, and regulatory bodies in low- and middle-income countries. It will require adequate systems for quality control and regulatory approval to assure consistent, high-quality products in the absence of first-world regulatory control, and legal systems within manufacturing countries that enable the supplier to effectively support its patent rights. To reach their goal, PDPs will need greater engagement of the scientific community and funding agencies in operational and health-services research, including mode and cost of delivery, patient acceptability and compliance, dosage and toxicity, and methods to adapt interventions to local conditions and integrate them into existing services.

4. CONCLUSIONS

Workshop presenters broadly endorsed the usefulness of bringing together diverse groups of practitioners to address the challenges of IP management for global health outcomes. The value of such a platform increases as the numbers of practitioners and institutions associated with PDPs expand. There is value in continuing broad discussion, as well as in more focused discussion with respect to specific issues, such as calculating price. From discussions at the workshop ideas emerged in regard to a number of actions that could both contribute to a wider understanding of issues surrounding intellectual property:

- developing best practice standards and disseminating these widely
- developing and disseminating case studies of various IP approaches related to market segmentation, tiered pricing, and royalties
- pursuing focused workshops on common issues such as pricing, product liability, early-stage licensing, and sponsored-research agreements with academe, or IP assembly and freedom to operate
- organizing inventories of IP rights held and the licensing status of these IP rights in key global health fields
- encouraging academic licensing practices that make products more accessible to impoverished populations and provisions within research sponsorship agreements that are responsive to the special requirements of PDPs
- supporting IP mapping and/or IP-landscape analysis for products of particular priority, or disseminating such landscapes where available
- instituting training programs and personnel exchanges to build research and technology management competencies and partnerships in low- and middle-income countries
- encouraging needed market analysis, such as estimates of need, to engage corporate interest

It is clear that many PDPs have matured over the past few years, progressing along the continuum from R&D to dissemination. Many have secured funding and negotiated successful deals, sometimes with numerous partners. Most, however, are still in the early stage of product development, and few have reached the threshold of product completion and distribution. Thus, there are no real outcomes to measure at this time. Moreover, deals are highly contextual. Still, although best practices will continue to emerge and be refined, a set of best principles or working tenets for ensuring product access and availability has clearly been established. In all cases, the role of intellectual property in PDP agreements is to provide incentives for private investment in public health and to structure and define the nature of the relationship among the partners with regard to how rights will be shared or exercised. There

is nothing particularly novel about the terms of agreements reached by PDPs; rather, it is their totality as a public/private hybrid that sets them apart. Collectively, the PDPs are broadening our creative understanding of practical ways to resolve the public-policy dilemma of balancing private incentives to generate needed R&D investment with the goal of access to those in need. ■

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1 Global Forum for Health Research. 1999. The 10/90 Report on Health Research. Geneva: Global Forum for Health Research

2 Mahoney R and CM. Morel. 2006. A Global Health Innovation System. *Innovation Strategy Today* 2(1): 1–12. www.bioDevelopments.org/innovation.

3 Other activities such as financing and capacity building are *crosscutting means* to address the components. They are not components of innovation in and of themselves.

4 See also Mahoney RT, A Krattiger, J Clemens and R Curtiss III. 2007. The Introduction of New Vaccines into Developing Countries IV: Global Access Strategies. *Vaccine* (in press).

5 25 and 26 July 2006 at the Aeras facility in Rockville, Maryland, U.S.A. The meeting included representatives of PDPs, industry, and academe, who shared their perspectives on IP issues, partnership strategies, and value propositions or incentives in deal making. The involvement of corporate and academic partners helped facilitate discussions about the dynamics that shape and direct successful public-private partnerships. For example, there is a strong interest on the part of the PDPs in building knowledge among university technology managers of the special needs and requirements of the PDPs as nonprofit enterprises. Correspondingly, PDPs can learn from university technology offices how to more effectively negotiate sponsored research or early-stage licensing agreements with universities, given the requirements and needs of academic environments.

6 To view the 2004 MIHR report, see: www.globalforumhealth.org/filesupld/ippph/dealmaking.pdf. The 2006 meeting, like its predecessor, provided a platform for exchanging emerging best practices in structuring and negotiating product development agreements for technologies needed in developing countries. Presentations centered on case studies of several PDPs to illustrate terms, conditions, and strategies that may be employed to help ensure product availability and access. Topics included: segmentation of markets, pricing, negotiating with universities, liability issues, ownership and use of clinical trial and regulatory data, partnerships with emerging suppliers, and technical assistance needs to ensure technology transfer. Discussions were focused on best practices for deal making in various contexts, from understanding complementarities of missions to negotiating contract language.

7 See, also in this *Handbook*, chapter 2.7 by J Oehler. See also Kaplan W. 2005. www.who.int/intellectualproperty/studies/W.Kaplan2.pdf.

8 See, also in this *Handbook*, chapter 17.9 by J Banerji and B Pecoul.

9 www.gavialliance.org.