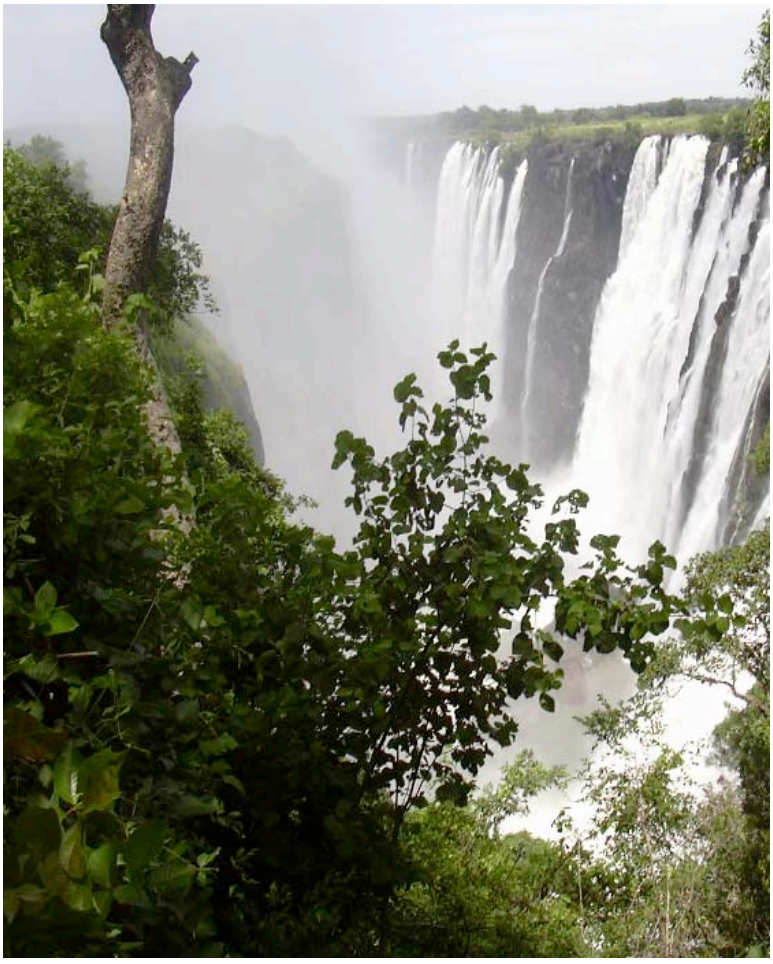
African Technology Development Forum

ATDF JOURNAL VOLUME 2, ISSUE 4

INNOVATION; TECHNOLOGY; TRADE; DEVELOPMENT



HIGHLIGHTS:

"There is no medicine like hope, no incentive so great, and no tonic so powerful as expectation of something better tomorrow"

(Orison Swett Marden)

ISSN: 1817-2008

Abbreviation:

Afr. Technol. Dev. Forum j

http://www.atdforum.org/

December 2005

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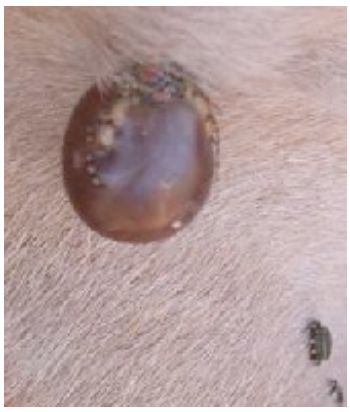

Wishing all our readers a prosperous 2006

Facilitating Humanitarian Access to Pharmaceutical and Agricultural Innovation

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Abstract

This paper seeks to raise awareness about the importance of managing IP to facilitate humanitarian use and applications. Our goal is to identify intellectual property approaches that can promote access to and use of health and agricultural product innovations by poor and disadvantaged groups, particularly in low-income countries. The paper encourages more public-sector IP managers to understand and employ strategies that will accomplish these goals. Humanitarian use approaches should become the norm, and we seek to help private-sector licensees understand the rationale and potential benefits behind such strategies. This paper focuses on the pharmaceutical and agricultural sectors, but the principles noted could potentially be applied to other areas as well.

There are key moments when technology managers can improve the likelihood that their IP will benefit people in need: when they decide 1) who will receive a license, 2) whether the license will be exclusive, 3) what types of applications will be covered, and 4) how long the duration of the license will be. In addition, if and when technology managers reach the stage of negotiating license terms, particularly in an exclusive license, they may be able to include legally enforceable provisions to protect in advance the possibility of sharing their IP with third parties for the benefit of people in need. These humanitarian license provisions may define beneficiaries by the field in which the IP would be applied, by geographic region, by national income level, or by market (e.g., "subsistence farmers"). License terms may also require the licensee to meet specific milestones related to availability or price in order to ensure that the IP benefits the target populations. The license agreement can further increase access through specific terms that govern the use of the technology for research, the licensee's freedom to grant sublicenses, and the treatment of follow-on innovations developed by the licensee.

We acknowledge that improved IP management cannot by itself solve the access crisis. Even if technology managers adopt humanitarian IP management strategies, they will need to connect with development partners who can utilize the protected technologies. In some cases, these partners may not yet exist. But when partners are found, it will be important to establish simple, efficient ways for them to identify technologies that public sector institutions are willing to share. We believe that the number and variety of technologies being managed with humanitarian goals in mind will continue to increase, and so the SIPPI project plans to explore ways to increase the transparency of license terms covering these technologies, thus making this information more widely available to potential beneficiaries

Patents and neglected markets

Intellectual property (IP) rights play an increasingly important role in the development, manufacture, and distribution of products in agriculture and health. During the past 25 years, there has been an unprecedented increase in the scope, level, role, geographical, and subject-matter coverage of IP protection.[1] Strong patent protection is intended to contribute to increased research investments and a favorable climate for technology transfer. But it may not always produce these effects. In fact, IP licensing practices may inhibit access to IP protected knowledge, research tools, and products.

The unmet medical and agricultural needs of developing countries are vast. Reflecting the technological and financial disparity between developed and developing countries, low- and middle-income countries account for less than 10% of worldwide research and development expenditures.[2] And despite increasing levels of investment in pharmaceutical R&D during the past 30 years, only 1% of new compounds marketed have been for developing world diseases.[3] Recent research has identified some increase in innovative activity related to diseases specific to poor countries, though this activity "remains extremely low relative to pharmaceutical research overall," and has resulted, in large part, from increased public R&D funding for global health.[4,5,] Similarly, private-sector agricultural research is more likely to focus on specialty crops of interest to developed countries than on staple crops that are important to resource-poor farmers in developing countries[6].

Objectives of this paper

Because certain patent arrangements can inhibit the development and dissemination of products for developing countries, we need to explore intellectual property management strategies that can help remove some of these obstacles. It is equally important to apply creative patent management strategies that actively promote access to needed products in developing countries. Care must be taken, however, to ensure that patents on research inputs do not discourage or unreasonably increase the cost for product development that targets needs in small or unprofitable markets.

Originally published in *Innovation Strategy Today* 1(3):203-216. www.biodevelopments.org/innovation/index.htm

The AAAS project on Science and Intellectual Property in the Public Interest convened a working group to explore these topics in 2004. Working group members contributed experience from the public and private sectors, representing both the agricultural and health fields. This paper draws upon expertise provided by all group members, but it is not necessarily endorsed by them.

The goal of this paper is to identify licensing strategies that promote humanitarian access to health and agricultural product innovations and their use by poor and disadvantaged groups, particularly in low-income countries. The paper encourages more public-sector IP managers to understand and employ strategies that will achieve these goals. We also seek to help private-sector licensees understand the rationale and potential benefits behind such strategies. Indeed, humanitarian licensing strategies should more and more become the norm.

Of course, improved IP management cannot by itself solve the access crisis. Increased investments in providing basic needs (food, clean water, and adequate sanitation), sound national policies, and improved health care and agricultural infrastructures are all essential components of greater global development and equity. Nevertheless, better IP management practices can contribute to the development and dissemination of essential medicines and agricultural technologies for developing countries.

This paper deals with voluntary strategies, but this is not meant to exclude other approaches, such as incorporating some of the suggested changes in IP management into public policies, laws, or treaty reform. The advantage of voluntary strategies is that they can be implemented immediately, without the complexities involved in changing regulations and legal requirements.

Background and related initiatives

Our discussion of strategies builds on the initiatives, experience, and proposals of other organizations for the management of IP. The UN Millennium Project Task Force on Science, Technology, and Innovation recommended expanding mechanisms for inventors to make their ideas available royalty-free for uses that meet the needs of poor countries, noting in its final report that "only a handful of mechanisms are designed to promote such activities."[7] However, beginning in the 1980s, and expanding through the 1990s and the early years of the 21st century, an increasing number of organizations have been using IP management practices to promote the health and food-security of underserved populations. These include the Program for Appropriate Technologies in Health (PATH) and the Population Council, as well as various other public and public-private partnerships, such as the International AIDS Vaccine Initiative, the Global Alliance for TB Drug Development, the Global Vaccine Initiative, the Diseases of the Most Impoverished Program of the International Vaccine Institute, and the Centre for the Management of Intellectual Property in Health Research and Development (MIHR). International entities (e.g., the World Health Organization) have undertaken humanitarian licensing, as have national entities such as the U.S. National Institutes of Health, which now includes humanitarian clauses in their licensing agreements as appropriate. Several governmental organizations in developing countries, such as the Council for Scientific and Industrial Research of India, are beginning to undertake humanitarian licensing. Agricultural organizations with relevant experience include the African Agricultural Technology Foundation, the International Service for the Acquisition of Agri-biotech Applications (ISAAA), and the institutes of the Consultative Group on International Agricultural Research (CGIAR).

One of the most noted examples of humanitarian IP management involves vitamin A-enriched "golden rice." Although developed mainly with public sector funding and research, around 45 patents associated with golden rice are owned by approximately 30 companies and public institutions in the US, and only a few patents are held in developing countries.[8] The inventors of golden rice licensed their inventions related to golden rice to Greenovation, a biotech spin-off company from the University of Freiburg, that is owned by the inventors themselves. Greenovation then exclusively licensed its golden rice-related patents to AstraZeneca (now Syngenta). Subsequently, Syngenta entered into a license agreement with the inventors that allowed them, and Syngenta, to license golden rice technologies to developing countries. Other companies holding golden rice-related patents also agreed to the same arrangement. That arrangement allows both Syngenta and the inventors to grant licenses—with the right to sub-license—to any *bona fide* research organization for the development of golden rice. The rice can be used royalty-free and allows farmers to earn as much as $10,000 per year from its sale. Higher sales would require farmers to acquire a commercial license from Syngenta.[9] The example of golden rice illustrates that it is possible to make IP available for research and commercialization in developing countries.

Yale University offers another example of humanitarian IP management. It holds a key patent on stavudine (d4T), a widely used HIV/AIDS antiretroviral drug. After Yale licensed this patent to Bristol-Myers Squibb to incorporate renegotiated humanitarian terms, allowing the drug to be subsequently licensed for generic production in South Africa. The university also negotiated a price cut, immediately reducing the price of d4T in Africa by thirty-fold. When the generic product came on the market, it further reduced the price by as much as 40%.

Other examples of humanitarian IP management include Cornell University's transfer of ringspot resistant papaya to Thailand, as well as several projects brokered by the International Service for the Acquisition of Agri-biotech Applications (ISAAA). The latter include local varieties of potato transferred from Monsanto to Mexico, as well as ringspot virus resistant and delayed ripening papayas transferred from Monsanto and Syngenta, respec-

tively, to Southeast Asia.[10] Finally, a recent agreement between Gilead Sciences and the South African drug maker Aspen Pharmacare is another example of humanitarian IP management for health products. Gilead will allow Aspen to produce generic versions of the HIV/AIDS antiretrovirals Truvada and Viread, and university inventors who own foundational patents for both drugs have agreed to waive royalties in the developing countries served by Aspen.[11]

Intended audience

This paper is written primarily for licensors, particularly university-based technology transfer managers and public-sector intellectual property managers, and secondarily for the staff of intellectual property departments in corporations with which these entities may enter into agreements or who may themselves decide to adopt some of the following strategies. Foundations or agencies that fund research and that may wish to encourage or require their grantees to engage in humanitarian IP management are another important audience.

Public Sector

Universities and public sector institutions play key roles in the development of medicines and agricultural products. Their roles are generally early in the process, and because university-based research is most often upstream, final products based on their research often involve significant development by others. The manner in which public sector researchers make their "upstream" technologies and research tools available can influence whether populations in developing countries have access to the end products of this research.[12]

In recent years a number of nonprofit public-private partnerships (PPPs) have formed with the mission of developing health and agricultural products for markets that are neglected by traditional for-profit R&D companies. These PPPs are typically funded by foundations or public sources and may receive in-kind support, or in some cases direct funding, from private companies.

Like typical drug companies, health-focused PPPs often develop a portfolio of candidate products, hoping that a few will be safe and effective enough to treat their focal condition. Examples of PPPs that develop pharmaceuticals are listed below. Entries were compiled from Gardner and Garner (2004)[13] and Merz (2005).[14]

If a university has already licensed IP to a company, renegotiating to provide access for a PPP can be costly and difficult—even if the PPP seeks to develop the invention into a non-competing product. However, the university can take steps at the beginning of the technology transfer process to facilitate the use of its invention for developing products that serve the poor. If a technology does not interest commercial licensees, university IP managers can seek PPPs or other non-traditional license partners to develop it for neglected markets. To be able to take advantage of these opportunities, it is very important for universities to establish policies and guidelines to manage university-generated IP for humanitarian use and applications.

Why should universities and public sector institutions take advantage of these opportunities to promote humanitarian use? Most universities and public sector research institutions seek to contribute to the well-being of humankind through their patenting and licensing activities. For example, each of the top four university recipients of U.S patents in 2004[15] states public benefit as an explicit goal in its patent policy:

University of California (#1 with 424 patents): "It is the intent of the President of the University of California, in administering intellectual property rights for the public benefit, to encourage and assist members of the faculty, staff, and others associated with the University in the use of the patent system with respect to their discoveries and inventions in a manner that is equitable to all parties involved."[16]

California Institute of Technology (#2 with 135 patents): "It is the policy of the Institute that such patents be used for the public benefit. If there are innovations or discoveries that result in the filing of patent applications and the acquisition of patents, the Institute intends to serve the public interest by prudent and appropriate efforts to transfer the technology to those who will facilitate public use."[17]

Massachusetts Institute of Technology (#3 with 132 patents): "It has long been acknowledged that the primary functions of a university are education, research, and public service. It is in the context of public service that M.I.T. supports efforts directed toward bringing the fruits of M.I.T. research to public use and benefit."[18]

University of Texas (#4 with 101 patents): "It is the objective of this policy to encourage the development of inventions and other intellectual creations for the best interest of the public, the creator, and the research sponsor, if any, and to permit the timely protection and disclosure of such intellectual property by development, commercialization after securing available protection for the creation, by publication, or both."[19]

Public funding agencies also seek to promote public benefit. The mission of the U.S. National Institutes of Health (NIH), for example, is to support biomedical research to extend healthy life by reducing illness worldwide. NIH therefore seeks to understand and overcome the obstacles hindering the public availability of inventions made by NIH scientists. To this end, NIH engages in a variety of forms of humanitarian licensing and humanitarian use agreements.[20] Many other public-sector actors and universities are also interested in "doing the right thing" in terms of promoting access, but they often do not know how to proceed.[21]

We anticipate that at least some types of humanitarian IP strategies will have little or no impact on licensing

revenues for the technology creators. Whether that will be the case may depend on whether humanitarian licensing becomes commonly practiced and accepted. It may be important for a university or research institute's administration to commit to humanitarian IP management as an extension of the institution's public mission. This might enable technology-licensing officers to risk sacrificing small amounts of licensing revenue when there is an opportunity to enhance product development initiatives for the poor. In addition, institutional administrations can foster approaches among technology licensing officers that would enhance such product development initiatives when financial promise is low.

Private Sector

Why address intellectual property managers in the commercial sector? Most technologies developed by universities and public-sector institutions are at early stages of development and require private companies to invest more in research and development to create practical applications. Universities generally license these early-stage technologies to the private sector. The success of humanitarian licensing therefore depends on the willingness of private sector actors to accept certain conditions and requirements that would increase access later in the product development and marketing stages.

We think there are two reasons that commercial licensees may support humanitarian licensing. First, commercial entities usually expect major financial returns in developed world markets, but developing country markets are often considered unprofitable. Hence, many types of humanitarian licensing may not harm the financial interest of the commercial licensee. Moreover, a corporation may advance its reputation for social responsibility and win greater esteem from the public by accepting humanitarian licensing.

Multinational companies have already shown a willingness to segment their markets and offer concessionary terms to facilitate access to their products in poor countries. A number of examples have been highlighted already, including AstraZeneca, Bristol-Myers Squibb, Gilead, Monsanto, and Syngenta. Activities by Chiron, GlaxoSmithKline, Pioneer Hi-Bred, and Roche are mentioned later

HUMANITARIAN LICENSING STRATEGIES

In this section we discuss some successful strategies and some new proposals for managing IP to facilitate humanitarian use and applications. These include case studies in which IP owners have used non-traditional IP management techniques to promote the development of products for neglected markets. In this section, we describe general approaches to licensing and some specific license features that a patent owner can use when transferring technology to a commercial entity.

PPPs that develop pharmaceuticals

Aeras: Aeras Global TB Vaccine Foundation
www.aeras.org

Children's Vaccine Programme at PATH
www.childrensvaccine.org

CONRAD
www.conrad.org

DNDi: Drugs for Neglected Diseases Initiative
www.dndi.org

FIND: Foundation for Innovative New Diagnostics
www.finddiagnostics.org

Gates Foundation/U. of North Carolina Partnership for the Development of New Drugs
www.ippph.org/index.cfm?page=/ippph/partnerships/name&thechoice=show&id=85&typobj=0

Global Microbicide Project
www.gmp.org

Global Vaccines Inc.
www.globalvaccines.org

Human Hookworm Vaccine Initiative at Sabin Vaccine Institute
www.sabin.org/hookworm_slides.htm

IAVI: International AIDS Vaccine Initiative
www.iavi.org

Infectious Disease Research Institute
www.idri.org

International Partnership for Microbicides
www.ipm-microbicides.org

iOWH: Institute for One World Health
www.oneworldhealth.org

IPM: International Partnership for Microbicides
www.ipm-microbicides.org

MMV: Medicines for Malaria Venture
www.mmv.org

MVI: Malaria Vaccine Initiative
www.malariavaccine.org

PATH: Program for Appropriate Technology in Health
www.path.org

PDVI: Pediatric Dengue Vaccine Initiative
www.pdvi.org

PneumoADIP. Pneumococcal Vaccines Accelerated Development and Introduction Plan
www.pneumoADIP.org

TB Alliance: Global Alliance for TB Drug Development
www.tballiance.org

Identifying the intended beneficiaries

Rights reserved or obligations set out to facilitate access in developing countries will need to specify the intended beneficiaries. In the end, all humanitarian licensing efforts should strive to benefit underserved people in developing countries by providing greater access to needed technologies. However, defining this population or identifying the institutions that could serve this population with the licensed technology may require different approaches, depending on the particular technology and requirements of the primary licensee. Below are some options for defining

the beneficiaries of humanitarian license terms.

A developing country can be defined in a number of ways, for example, by reference to the United Nations list of "least developed countries," geographically, or by reference to lists provided by OECD countries, the World Bank, or the Food and Agriculture Organization (FAO). Countries may also be mutually agreed to by the contracting parties, who may also need to decide whether the agreement will cover middle-income as well as low-income countries.

In addition to or in place of defining a list of countries covered by the reservations and/or exemptions in a humanitarian license, negotiators may wish to further define the population in those countries that would be covered. The intended population might be the "poor," "those in need," subsistence farmers, populations in geographically underserved regions, or a certain market segment.

A market segmentation or dual market approach is often used to target intended beneficiaries and is involved in many of the strategies discussed in this paper. With this approach, an exclusive license might give a private sector entity the sole right to use a technology in profitable markets, while allowing others to use the technology at no cost or reduced royalties to serve market segments that do not interest the private sector.

In the licensing arrangements for golden rice, a humanitarian use clause was used to segment access to an agricultural technology, committing the owners of key proprietary components to donating their technology to the "poor." Negotiations over how exactly to define and make operational such "donations" are ongoing. These negotiations focus on defining the humanitarian use market and ultimately on the precise wording of the humanitarian use clause. This humanitarian use clause will determine who qualifies as a beneficiary of royalty-free access to golden rice and exactly how they would benefit.[22]

AGERI and Pioneer Hi-Bred *bt* maize in Egypt

Strategy employed: *dual market agreement*

The public-sector Agricultural Genetic Engineering Institute (AGERI) in Egypt owns patents covering a technology for producing insect-resistant maize via the insect toxin *Bacillus thuringiensis* (*Bt*). AGERI allowed the US company Pioneer Hi-Bred to evaluate some of these patented proteins and genes, and in exchange Pioneer Hi-Bred trained AGERI scientists in methods for characterizing *Bt* and maize transformation technologies. The Agricultural Biotechnology Support Program of the US Agency for International Development supported the project. Now, AGERI is commercializing the technology in Egypt while Pioneer has commercial rights in the US.

Source: Margarita Escalar, "Public-private partnerships in modern biotechnology," 2002 SciDev.net Policy Brief. Available at: www.scidev.net/dossiers/index.cfm?fuseaction=policybrief&policy=32&section=112&dossier=6

Although market segmentation strategies have been employed successfully,[23] certain challenges remain, namely the containment of the IP within the targeted markets. In addition to the humanitarian transfer of products to the intended populations (i.e., markets that may not necessarily be lucrative for large companies but nevertheless present niche opportunities for smaller companies), many developing countries may also have emerging private markets for the same goods. Market segmentation might be most successful where noncommercial markets can be sharply delineated by region, which makes it easier to exclude spillovers to non-targeted markets.[24] In addition, market segmentation often requires intense negotiation, the development of trust between partners, and the capacity to enforce agreements.

Non-exclusive licensing

In non-exclusive licensing, in addition to the primary license agreement, the licensor retains the freedom to license the technology to other parties. Some institutions (e.g., NIH) seek to use non-exclusive licensing or to license to multiple companies whenever possible. If a university can accomplish technology transfer to a company using non-exclusive licensing, it is free to subsequently license the technology for humanitarian applications. Sometimes a commercial licensee insists upon an exclusive license, in which case public-sector licensors may limit the exclusive license to developed-country markets (as discussed later) or for specific product applications.

Transferring technology to public-private partnerships (PPPs)

When it is clear that a technology could benefit neglected markets (e.g., a low-cost HIV diagnostic or an agricultural trait important for subsistence agriculture), university technology managers may be able to transfer the technology to a nonprofit corporation for product development either on an exclusive or non-exclusive basis. The business models of PPPs vary. Some conduct in-house product development; others manage collaborative development by public and private sector labs. The transfer of technology could take forms ranging from direct licensing or donation of a patented invention to contributions of know-how or scientific expertise.

Another possible model is an arrangement in which a commercial licensee focused on markets in affluent countries makes the technology available to a PPP on concessionary terms for marketing or development for poor countries. In order to minimize transaction costs for the PPP, it is highly preferable for the university to engage with the nonprofit developer before completing negotiations with the commercial licensee.

University technology managers can also facilitate nonprofit product development efforts by offering PPPs own-

Finding New TB Treatments

Strategies employed: *licensing to PPPs and reduced royalties in developing countries*

Over the past 40 years, virtually no investments have been made to develop new products for TB, and the standard course of treatment remains very long and cumbersome. However, many new compounds have been discovered by drug researchers in the interim, and the TB Alliance is reviewing some of the most promising for potential use against TB. Half of the compounds have come from universities, and the others from industry—licensed on concessionary terms. For example, the TB Alliance obtained an exclusive worldwide license to PA-824 and related compounds from Chiron Corp. under an agreement that eliminates royalties for drugs marketed in impoverished countries.

Source: TB Alliance website. Available at: www.tballiance.org/3_1_2_AportfolioofDrugCandidates.asp

CDA malaria treatment

Strategies employed: *PPP-sponsored product development and preferential pricing requirement*

The WHO Tropical Disease Research program, the Medicines for Malaria Venture (MMV), and GlaxoSmithKline have formed a partnership to build upon the two-drug anti-malarial Lapdap by adding artesunate to the combination. The new therapy will be called CDA, for its ingredients chloroproguanil, dapsone, and artesunate. The original Lapdap was conceived by scientists from the Wellcome Trust Laboratory in Nairobi and the University of Liverpool, then brought to market by a public-private partnership involving MMV, British universities, the Wellcome Trust, GlaxoSmithKline, and the UK Department for International Development. It was approved by the UK Medicines and Healthcare Products Regulatory Agency in 2003. Under the agreement for developing the new triple-drug combination, it will be made available at preferential prices to the public sector in malaria endemic countries.

Source: TDR News No. 72. 2004. "Artesunate combinations are coming: partnership develops Lapdap plus artesunate." Available at: www.who.int/tdr/publications/tdrnews/news72/lapdap.htm

ership of patents that the university no longer wishes to maintain. Even when a technology does not appear to have a clear application for developing regions, it may prove useful for some aspect of the PPP's work to develop products for these regions.

Transferring technology to companies in developing countries

Technology managers may seek commercial partners in low- or middle-income countries to develop technologies that address conditions specific to those regions. These companies are likely to have greater interest in developing products that meet the needs of these countries than commercial entities in wealthier countries. They may also be able to develop, produce, and distribute the product at much lower cost than typical partners in the U.S. or other industrialized countries.

Out-licensing

Out-licensing is primarily executed by drug companies that are already producing name-brand versions of a patented drug, but universities could negotiate with corporate licensees to ensure that out-licensing to generic companies takes place. Under the out-licensing approach, drug patent holders award non-exclusive licenses to generics manufacturers, allowing them to produce cheap copies of drugs for sale exclusively in designated poor countries. The generic makers are prohibited from selling products in the patent holder's developed country markets, and they may be required to modify their packaging so as to discourage re-importation by making the generic versions easier for customs officials to identify. Generic producers pay a royalty to the patent holder, and are encouraged to compete on price. An advantage of this semi-cooperative approach is that generic makers in developing countries can get more information from the patent holder than just the patented technology itself, such as manufacturing expertise and regulatory data. In the rare case that a university holds IP that needs little additional development, it could essentially make the out-licensing arrangement itself by licensing the patent to a name brand pharmaceutical company for wealthy markets and to generic manufacturers for production in developing countries. It may be more difficult, though not impossible, to encourage the sharing of manufacturing expertise and regulatory information.

Conditions in funding agreements

Foundations, government agencies, and other organizations can require that funded work be licensed under humanitarian terms by inserting conditions into funding agreements. Establishing humanitarian IP management conditions in advance can simplify later negotiations, help researchers and IP managers plan ahead, and increase the prospects of success. The Rockefeller Foundation has crafted language to include in research agreements for this purpose, offering a model for ways that funders can increase humanitarian access to the research supported by their grants. The Rockefeller Foundation requires grantees, whether or not they claim or obtain patents or other proprietary rights in their discoveries, "to license or otherwise make available the Discoveries to third parties in the commercial and public sectors (to the extent permitted under the MTAs) for the purpose of furthering the creation, reproduction, modification, and/or sale of the improved end product."

Positive humanitarian conditionality in licensing agreements

Licensing conditions may require the licensee to do specific good things to benefit disadvantaged populations. These conditions are sometimes referred to as

"white knight clauses." These may include marketing a product in developing nations at a reduced royalty or price, donating materials for clinical trials, or cooperating with a humanitarian licensee in a specified way (e.g., by providing clinical or field trial results). A licensor could also insert language requiring the licensee to make products developed from improvements to the technology available in low- and middle-income countries at a reduced cost.

The US National Institutes of Health (NIH) often uses these clauses in its agreements to ensure that the licensee undertakes specific actions to benefit the public sector (e.g., mandating the supply-back of licensed products or services, health education programs, indigent access programs, reduced royalties for developing countries, biodiversity compliance for natural products, and other means of ensuring developing country access for licensed products). NIH also requires licensees to create a worldwide development and marketing plan to facilitate developing country access to licensed products, the implementation of which it monitors through agreed upon benchmarks.[25]

Performance milestones

A milestone is a performance requirement on the part of the licensee. Milestones are often used in public-private partnerships and sponsored research agreements to measure a project's progress and success. An example of a humanitarian licensing milestone might be a requirement that on or before the date of the first phase of a clinical trial for a new drug, the licensee will have identified a generic manufacturer in a middle-income country to produce the licensed technology at a reasonable price for developing countries. Subsequently, if this milestone is not met, other provisions and reservations in the agreement would be triggered, for example loss of exclusivity, sublicensing, exercise of march-in rights, and even termination of the agreement.

Ensuring accessibility through pricing

To help ensure access to products, the licensor may require that any product developed and brought to the market be distributed at a reasonable price. Despite the inherent difficulties in defining what is reasonable, price is a readily measurable condition that is easier to monitor than more broadly defined requirements concerning access.[26] This model could be expanded whereby licenses to companies include an appropriate balance of incentives to the licensee and market access for the poor. Licensees might be required to meet certain milestones, such as government procurement targets in defined countries and at prices that are deemed appropriate for that market. Here, an appropriate price may be defined as the cost of production plus a small profit, usually in the 5-10% range prior to being allowed to commercialize the product in more lucrative markets.[27] To ensure that an appropriate price is reached and maintained, the licensor may also include contractual language that mandates the submission of manufacturing cost reports and product cost calculation details on a regular basis.[28]

Reserving rights in license agreements

Developing a Low-Cost Malaria Treatment

Strategies employed: *agreeing on IP management conditions in advance*

A research group sponsored by the Medicines for Malaria Venture (MMV) has developed a promising, low-cost malaria treatment known as OZ277 /RBx11160. MMV supported collaboration between scientists at the University of Nebraska, Swiss Tropical Research Institute, Monash University, and the Roche Company to develop OZ. The drug incorporates some chemical features of the plant-derived antimalarial artemesin, but can be produced through synthetic chemical processes, making it significantly cheaper. Patents covering OZ have been assigned to MMV, and MMV has engaged the Indian drug manufacturer Ranbaxy to further develop it. Upon regulatory approval, Ranbaxy will distribute OZ at low cost in malaria endemic countries. MMV facilitated arrangements for patent, royalty, and pricing structures to benefit those in need by establishing an IP management plan with its collaborators in advance. Below are excerpts from the "Statement of MMV Collaborative Principles":

MMV's central objective is to ensure the sustainable and continuous generation of appropriate new malaria medicines that are accessible to all of those in need in developing countries at the lowest prices practicable.

MMV requires intellectual property rights on a royalty-free basis to the relevant intellectual property, in the field of malaria, and developed through the collaboration.

MMV will seek the right to the relevant background intellectual property necessary to achieve the objectives identified herein.

MMV would not *normally* have a desire to retain any interest in relevant intellectual property rights for use outside the field of malaria or to constrain such use by its collaborators.

Source: Medicines for Malaria Ventures. "Statement of MMV Collaboration Principles." Personal communication, J. Carl Craft, Chief Scientific Officer, MMV. See also "Ranbaxy and MMV Achieve Potential Breakthrough in Malaria, Drug Enters Human Trials Phase." Ranbaxy Lab. Press Release, 18 August 2004. www.ranbaxy.com/newsroom/pressrelease_det.asp?sno=169

It is important to think through how the humanitarian purpose licensee will actually use the technology and to reserve an appropriate set of rights and exemptions. For example, the negotiators will certainly want to consider the scope of research rights and, depending on the particular technology and application, the scope of international trade rights. The humanitarian licensee might need the right to carry out research or manufacture within the commercial licensee's territory, so long as the research is done only for developing nation needs or the manufacture for export to developing nations. The commercial licensee may then wish to be protected against re-export into its primary commercial market. As noted earlier, the humanitarian licensee may also need rights for commercial use in low- and middle-income regions. Although the reservation may be defined as "humanitarian use," licensors may wish to consider additional, more specific reservations as described below.

Research exemption

One of the several goals of humanitarian IP management is to encourage research to develop products appropriate to the needs of the developing world. To this end, licensors could opt to insert a research exemption clause into licensing agreements that exempts specified categories and types of research from patent infringement in using its proprietary technologies, (e.g., to develop products that broadly benefit the public or the population of poor countries). The University of California technology transfer office is beginning to insert such research exemption clauses into licensing agreements. Other universities already reserve research rights for academic institutions in their standard exclusive licensing agreements (e.g., Stanford, whose standard license language is reproduced here). Such a clause could facilitate humanitarian use of the technology if it also reserved rights for nonprofit research institutions developing products for use in developing countries.

Sublicenses for developing countries

Unless provided for in the agreement, a licensee generally does not have sublicensing rights. Should the parties agree to allow sublicensing, the main agreement should specify the rights and obligations of the licensee with respect to the sub-licensee(s). In allowing for sublicenses, consideration should be given to the possibility of the original licensee entering into sublicenses inconsistent with the humanitarian goals of the agreement. This should be restricted. It is general practice for the licensor to hold the licensee responsible for assuring that the sub-licensee fulfils all the requirements of the principal license. The best way to ensure that the sub-licensee has obligations comparable to the licensee's is for the licensor to draft the sublicense terms. The licensor can thus be certain that all the humanitarian requirements within the primary agreement are included.

March-in rights

A licensor may wish to reserve march-in rights if the humanitarian purposes or milestones embodied in the agreement are not met (e.g., revoking a license or sublicensing to third parties in order to assure access).

Developing a Portable HIV diagnostic

Strategy employed: *condition in funding agreement*

When technology transfer officers at Massachusetts General Hospital and the University of Texas were licensing a prototype HIV diagnostic device to a start-up company, the requirements of the foundation funders allowed the foundations to grant additional licenses to entities capable of meeting charitable objectives in LDCs. Since it is a portable device, the technology could provide inexpensive and practical means of diagnosing HIV in resource-poor settings.

Source: Holly Foskett, Rebecca Menapace, Seema Shah Basu. "Developing Inventions for Neglected Diseases." Poster Presentation, 2003 AUTM Annual Meeting.

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Yale d4T Treatment for HIV

Licensing to producers in developing countries, Amending existing agreements

Yale University, which holds a key patent on stavudine (d4T), a widely used antiretroviral drug, renegotiated an agreement with its licensee Bristol-Myers Squibb to incorporate humanitarian terms that allowed the drug to be licensed for generic production in South Africa. This reduced the price of d4T in Africa by thirty-fold.

Treatment of future rights in license agreements

Reach-through Clauses

Reach-through clauses attempt to reach beyond the licensed technology and to ensure that the licensee treats new technologies, developed through use of the licensed technology or under a cooperative agreement, as subject to the same kinds of development obligations covered by the original license. This type of clause is often used by public-private partnerships to encourage the development of specific technologies that benefit developing nations while allowing the private-sector partner to benefit in the developed world.

Licensors can also help make inventions more available to populations in need by insisting on certain terms when licensing inventions to commercial partners. Opportunities to transfer technologies to be developed by public-private partnerships or by other organizations can also be pursued.

Grant back clauses

If it is likely that the commercial licensee will develop improvements to the technology, it would be wise to require that the licensee grant back non-exclusive rights to those improvements. This would ensure that they would be available later for a humanitarian purpose licensee. The same might go for access to test results or regulatory data. If either party is concerned about liability issues, there might be, for example, requirements for any humanitarian licensee to be adequately insured or to be operating in compliance with relevant regulations.

Amending existing agreements

While the goal of this document is to promote humanitarian licensing from the outset, when agreements already exist they can also be amended or revised to meet humanitarian needs. There are several examples of successful renegotiations. For example, the humanitarian license mentioned earlier between Yale University and Bristol Myers Squibb was actually the result of a renegotiation of their license for the AIDS drug d4T, which permitted generic d4T to be made and used in South Africa. There are also examples from the agricultural sector in which parties successfully addressed barriers posed by a worldwide exclusive license between a university and a company. In one case, a company insisted that no license was required to use the licensed technology in a certain country. It stated this in a letter that permitted the university to transfer a gene construct directly to the country. In general, renegotiating license terms is not desirable because it increases transaction costs, delays projects, and may not always succeed. However, while there are clear benefits to addressing these issues upfront wherever possible, the fact that an agreement has already been concluded should not discourage participants from revisiting the agreement when an unforeseen need arises.

Proposals for New Approaches for Humanitarian Licensing of IP

Two new proposals conclude our discussion of specific strategies for humanitarian licensing: 1) considering a shorter length for an exclusive license and 2) equitable access licensing.

Shorter lengths of license exclusivity

Instead of granting exclusive licenses that match the term of the patent, the licensor can grant licenses for shorter periods, allowing access by multiple licensors over the life of the patent. There may be practical complications to this approach, since universities often receive patent cost reimbursements from licensees, which in turn require exclusivity until expiration of the patent term. Granting short-term exclusive licenses would likely require the university to bear all the costs related to maintaining and enforcing the patent, which it could only afford to do if the patent itself was bringing in significant licensing revenues. In that case, the university may be reluctant to end its licensing relationship with the high-revenue licensor.[29]

Equitable access licensing

Universities can also make use of an equitable access license to create enabling conditions for competition in low- and middle-income countries. An equitable access license 1) ensures freedom to operate for any party that manufactures and distributes the licensed technology and any derivative products in low- and middle-income countries, and 2) minimizes administrative overhead and political contingency by initiating a self-enforcing open licensing regime. In such a license, a university and licensee agree that any licensed technology, as well as licensee improvements (including improvement patents and registration data), for sale into low- or middle-income countries will be openly licensed to any company that meets Good Manufacturing Practice[30] standards. This arrangement allows multiple producers (including producers in high-income countries) to compete to produce low-price products for sale only in low- and middle-income countries simply after notifying the parties to the license.

The Equitable Access License developed by Universities Allied for Essential Medicines (UAEM) includes a humanitarian research clause to encourage research on neglected diseases. It provides that any party may pursue research anywhere in the world using the university technology and licensee improvements without paying a royalty, if the research targets a neglected disease in the U.S.[31]

Stanford Reservation of Academic Research Rights in Standard License Agreement

Strategy: *reservation of research rights*

3.4 **Retained Rights.** Stanford retains the right, on behalf of itself and all other nonprofit academic research institutions, to practice the Licensed Patent and use Technology for any purpose, including sponsored research and collaborations. Licensee agrees that, notwithstanding any other provision of this Agreement, it has no right to enforce the Licensed Patent against any such institution. Stanford and any such other institution has the right to publish any information included in the Technology or a Licensed Patent.

Source: Stanford Office of Technology Licensing, Available at: otl.stanford.edu/industry/resources/exclusive.pdf

Next Steps for AAAS Humanitarian IP Management Initiative

This document emphasizes the importance of managing public sector IP to facilitate humanitarian use and applications. It seeks to raise awareness about some of the techniques that have been pursued so far, and we are optimistic that additional approaches will emerge as more institutions undertake IP management with humanitarian use and applications in mind. We certainly do not mean to preclude other options.

Even if technology managers adopt humanitarian IP management strategies in the construction, negotiation, and formalization of legal agreements, they will also need to connect with development partners who can utilize the protected technologies to serve unmet needs in developing countries. In some cases, these partners

may not yet exist. But when they do, it will be important to establish simple, efficient ways for them to identify technologies that public sector institutions are willing to share.

We believe that the number and variety of technologies being managed with humanitarian goals in mind will continue to increase, and so the SIPPI project plans to explore ways to increase the transparency of license terms covering these technologies, thus making this information more widely available to potential beneficiaries

Acknowledgemnet:

* This work was supported by grants from the MacArthur and Rockefeller Foundations. The authors would like to thank all members of the SIPPI Working Group on Humanitarian Licensing for input on earlier drafts of this paper. Members of the working group included: Nalini Anand, Fogarty International Center, NIH; Usha Balakrishnan, University of Iowa; John Barton, Stanford Law School; Alan Bennett, University of California, Davis and PIPRA; Cathy Garner, MIHR; Robert Horsch, Monsanto Company; Amy Kapczynski, Yale University; Anatole Krattiger, Arizona State University, MIHR and Cornell University; Richard Mahoney, Arizona State University and MIHR; Duncan Matthews, Queen Mary Intellectual Property Institute, University of London; Luis Salicrup, Office of Technology Transfer, NIH; Joelle Tanguy, Global Alliance for TB Drug Development; and Jacob Werksman, Rockefeller Foundation; AAAS Staff: Audrey Chapman, Stephen Hansen, and Amanda Brewster. A staff member from Eli Lilly and Co. attended the first meeting of the working group. We also appreciate the inputs of the following people for their comments in later stages of its drafting: Nalini Anand, NIH; Usha Balakrishnan, University of Iowa; J. Carl Craft, Medicines for Malaria Venture; Amy Kapczynski, Yale University; Richard Mahoney, Arizona State University; Duncan Matthews, Queen Mary Intellectual Property Institute, University of London; Jake Werksman, Rockefeller Foundation; and Katherine Woo, Institute for OneWorld Health.

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1. Commission on Intellectual Property, *Integrating Intellectual Property Rights and Development Policy* (London, 2002), p. 2. www.iprcommission.org/papers/pdfs/final_report/CIPRfullfinal.pdf

2. Ibid., p. 1

3. Priya Shetty, "More Creative thinking needed on Drug R&D," 3 May 2005 editorial, SciDev.net: www.scidev.net/content/editorials/eng/more-creative-thinking-needed-on-drug-rd.cfm

4. Jean Lanjouw and Margaret MacLeod. 2005. "Statistical Trends in Pharmaceutical Research for Poor Countries." Commissioned by the WHO Commission on Intellectual Property, Innovation, and Public Health. www.who.int/intellectualproperty/studies/stats/en/index.html The authors found an increase in indicators of innovative activity (patenting and bibliometric citation) related to some diseases specific to developing countries between 1980 and 2002, but only the subset still in need of better, low-cost treatments. The authors found a downtrend in innovative activity among the subset for which treatments already exist. The authors suggest that although the increase in innovation coincides in part with the introduction of stronger patent protection in developing countries, increased public R&D funding for global health and political developments are likely to have made significant contributions over the same interval. Still, drug innovation targeting developing countries remains a tiny fraction of drug innovation overall.

5. Mary Moran. 2005. "A Breakthrough in R&D for Neglected Diseases: New Ways to Get the Drugs We Need." PLOS Medicine Vol. 2, Issue 9. The author reports an increase in neglected disease drug development projects since the year 2000, including activity by multinational companies, small companies, and PPPs. She observes that "commercial incentives were largely irrelevant to the decision by multi-national companies to re-enter the neglected disease field, while small companies involved in neglected disease R&D were indeed responding to commercial drivers. In most cases, the involvement or planned involvement of PPPs was crucial to company involvement, commercial or otherwise."

6. See the discussion of these issues on the website of PIPRA: www.pipra.org/main/purpose.htm

7. UN Millennium Project 2005. *Innovation: Applying Knowledge in Development.* Task Force on Science, Technology, and Innovation, p. 170.

8. Contrary to the often quoted 70-plus patents, Kryder, Kowalski and Krattiger (2000) clearly showed that the 70-plus patents included patent applications and patent families in different countries. Only 45 unique patents were identified at the time. Kryder, R.D., S. Kowalski and A.F. Krattiger. 2000. The intellectual and technical property components of pro-Vitamin A rice (GoldenRice™): A Preliminary Freedom-to-Operate Review. *ISAAA Briefs* 20. pp. 74. www.isaaa.org

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20. Luis Salicrup, Rachelle F. Harris, and Mark L. Rohrbaugh, "Partnerships in Technology Transfer: An Innovative Program to Move Biomedical and Health Technologies from the Laboratory to Worldwide Application," *IP Strategy Today*, 12 (2005): 1-12. www.biodevelopments.org/ip/ipst12.pdf

21. Kapcynski, p.7.

22. Lybbert, p. 18.

23. For example, a Monsanto and Kenyan Agricultural Research Institute agreement for unrestricted use of a transgene for the control of sweet potato feathery mottle virus in African sweet potatoes, and insect resistant maize with proprietary technologies is being transferred from Syngetna to Africa but cannot be used outside of the region; IRRI negotiated the rights for use of a stem borer resistance gene for rice from Plantech for all developing countries as defined by the UN. (from Byerlee and Fischer 2001, p. 14).

24. Derek Byerlee & Ken Fischer, Accessing Modern Science: Policy and Institutional Options for Agricultural Biotechnology in Developing Countries, *IP Strategy Today*, No. 1-2001, p. 18. www.bioDevelopments.org/ip

25. Mark Rorbaugh, "Technology Transfer to Benefit Public Health in LDCs," presentation made at Global Health & Technology Transfer Meeting, NIH Office of Technology Transfer, March 15, 2005.

26. Kapcynski, p.9.

27. The Concept Foundation (CF) has been pioneering in licensing that helps to ensure access through appropriate pricing mechanisms. It has partnered with 10 different PPPs with pharmaceutical companies worldwide. It has licensed technology to nine manufactures in five developing countries. CP has had products manufactured in eight countries and made available in more than 30 developing countries. Its first product, Cyclofem®, an injectable hormonal contraceptive, was made available to public sector health services in 1993. Since then, over 140 million doses of Cyclofem have been manufactured and distributed by CF licensees worldwide. Around 16 million HIV rapid tests have been distributed by CF licensees to public sector health services worldwide as well. www.conceptfoundation.org

28. Joachim Oehler, "The Role of Milestones in Licensing Deals to Assure Access to Health Products in Developing Countries," *IP Strategy Today,* No. 10-2004, p. 68. www.bioDevelopments.org/ip

29. Personal Communication, Usha Balakrishnan, Director, MIHR-USA. www.mihr-usa.org

30. WHO established a detailed set of Good Manufacturing Practice (GMP) standards, and many individual countries maintain their own GMP requirements for regulatory approval.

31. A. Kapczynski, "An 'Equitable Access License' for Use by Universities," Universities Allied for Essential Medicines.

AMMENDMENT OF WTO'S TRIPS DEAL TO ALLOW IMPORT OF GENERIC DRUGS

On 6 December 2005 WTO Members agreed to amend the TRIPS agreement to allow countries with insufficient pharmaceutical manufacturing capacity to import generic versions of drugs still under patent. The Decision spells out the conditions under which countries without pharmaceutical manufacturing capacity can import generic versions of drugs still under patent.

Source: Times of China

WTO Director-General Pascal Lamy hailed it as confirmation that "Members are determined to ensure the WTO's trading system contributes to humanitarian and development goals."

Civil society groups on the other hand expressed disappointment with the deal. Médecins Sans Frontières (MSF) warned that the amendment is "based on a mechanism that has failed to prove it can increase access to medicines."

The African Group at the WTO originally claimed that the conditions required by the waiver were too burdensome to be of practical use. In December 2004, it had proposed a 'lighter' format of the waiver that received criticism from some developed countries. African countries had to move away from this proposal in order to find a compromise with the United States.

The mechanism in question is a waiver of certain TRIPS obligations that allows countries to export drugs produced under compulsory licence, subject to a large number of conditions in both the exporting and importing country assuring that it would not be misused, for example to divert low-cost medicines into rich country markets.

However, even though several would-be exporters, such as Norway, Canada and India have altered their domestic laws to meet the waiver's conditions, and similar changes are imminent in the EU and Korea, not a single country has used it to import drugs. This is often blamed on the 30 August Decision's complicated eligibility requirements.

According to WTO rules, the amendment will only enter into force once it is accepted by two-thirds of the Membership. Pending such acceptance, the waiver will continue to be the legal basis for any trade in generic drugs produced under compulsory licence.

If the two-thirds requirement is not reached by December 2007 -- the deadline for acceptance by Members set by the General Council decision -- Members could extend it to a later date.

Civil society unimpressed

The amendment has made permanent a burdensome drug-by-drug, country-by-country decision-making process, which does not take into account the fact that economies of scale are needed to attract interest from manufacturers of medicines. "MSF has been seeking to make use of the mechanism by placing an order with a generic drug manufacturer, and has described the process to be very 'long' and 'resource intensive."

Nevertheless, 31 non-governmental organisations (NGOs) have issued a public statement urging governments to test the mechanism before turning it into permanent law. See the NGO statement in: http://www.cptech.org/ip/wto/p6/ngos12032005.html

Source: ICTSD reporting; "WTO TRIPS Council meeting -- Bad deal expected, THIRU BALASUBRAMANIAM (http://fromgeneva.blogspot.com/), 6 December 2005; "External Opposition Rises to TRIPS And Public Health Deal," INTELLECTUAL PROPERTY WATCH, 6 December 2005; "African Countries Ready to Accept TRIPS and Public Health Deal," INTELLECTUAL PROPERTY WATCH, 6 December 2005; "WTO OKs measures to improve drug access," ASSOCIATED PRESS, 6 December 2005; "Amendment to WTO TRIPS Agreement Makes Access to Affordable Medicines Even More Bleak," MÉDECINS SANS FRONTIÈRES PRESS RELEASE, 6 December 2005.

The final Decision and the Chair's statement are available at http://www.ictsd.org/iprsonline/index.htm.

Pharmaceuticals in the News

Pharmaceutical company focuses on neglected disease with new manufacturing investment in Africa

GlaxoSmithKline (GSK) announced it will manufacture the tablets for what is on track to be the largest drug-donation program in global pharmaceutical industry history, to eradicate lymphatic filariasis (LF) over a 20-year period.

Its chief executive said he was impressed after seeing the program in action in Ghana which has reached its target of treating all 10 million people at risk from the disease. GSK has been working with the World Health Organization for the past 7 years on a program to eliminate lymphatic filariasis by halting the transmission of the disease.

LF threatens over 1 billion people in 80 countries and 120 million people are already affected, 40 million of whom are seriously incapacitated and disfigured by the disease. "To date 12 countries have launched LF elimination programs in Africa reaching over 20 million people. These annual mass drug administration efforts have resulted in a significant decline in the level of infection. Today, I am calling for the other 27 countries which are endemic with LF in Africa to sign up and help transform the lives of millions of people.

"The world rightly focuses much attention on AIDS, TB [tuberculosis], and Malaria, but we mustn't fall into the trap of forgetting those diseases, such as LF, which cause enormous suffering and poverty. With the right will and with continuing efforts, LF could be the second disease in history to be eliminated."

Source: Drug Week via NewsRx.com Dec 09, 2005

New Malaria Drug Backfires

The fight against the killer malaria disease appears to have hit a snag as the newly approved drug, a combination of Artesunate and Amodiaquine is having diverse side effects on its users. The new drug, which is supposed to be the last stop treatment for malaria parasite was recently launched amid wild publicity and choreographed songs of joy among women and children. But little did they know that they were being used as 'guinea pigs' and that the drug was going to inflict pain on its users.

Public Agenda investigations have revealed that at least, a student of the Pantang Nursing Training College has died after experiencing severe reactions from the new malaria drug. According to the Deputy Nursing officer at the Accra Psychiatric Hospital, Mr. David Maculey, the student developed severe reactions from the drug including skin rashes, sore mouth and dizziness and died days after taking the drug.

In most of the cases, the conditions of the patients deteriorated within twenty-four (24) hours of taking the drug, subsequently resulting in their admissions into intensive care.One case that has received some prominence is that of John Nketia, a patient whose personal experience was published on page 9 of the Saturday December 10, 2005 edition of the Daily Graphic. The article raised a number of questions bothering on the efficacy and suitability of the drug.

However, adverts continue to run on our television and radios, extolling the good side of the rather deadly Artesuante Amodiaqine The question is will the drug be withdrawn or be allowed to kill many more people since, importers invested billions of cedis to import it.

Source: allafrica.com Dec 16, 2005

Biggest Egyptian Pharmaceutical Company on Sale

The Egyptian Ministry of Investment announced that preparations are underway to sell 10%-35% of the government's stakes in the Sayed Pharmaceuticals Company, one of the biggest pharmaceuticals companies in Egypt, through the local stock exchange, as of early January 2006. The ministry added that this decision came following a meeting of the general assembly of the Holding Company for Pharmaceutical Industries. The Egyptian pharmaceutical industry is considered one of the oldest strategic industries in the country. It was founded in 1939 with the establishment of Misr Company for Pharmaceutical Industries. The industry developed slowly between the 1960s and 1980s, following nationalization schemes which brought the industry under full government control. With the launching of reform programs in 1991, pharmaceutical companies gained greater autonomy and an increasing number of private sector companies entered the market. At present, there are 30 pharmaceutical-producing companies of which eight are public and 22 private.

Source: Al-Sharq Al-Awsat newspaper (December 8, 2005)

Seroprevalence of rubella antibodies among antenatal patients in South Africa is reported

According to a study from South Africa, "To determine the seroprevalence of rubella virus infection among antenatal patients aged between 15 and 45 years in the Western Cape province of South Africa, in order to provide data to determine the need for vaccination to protect women of childbearing age, 1,200 provincial serum specimens from participants in the 2003 Department of Health antenatal HIV/syphilis serosurvey were selected from the four districts of the Western Cape." "The specimens were age-stratified and screened qualitatively for rubella immunoglobulin G (IgG) antibodies by means of a commercial immunoassay during October 2004," said Craig Corcoran and colleagues at the University of Cape Town. "Within the Western Cape a total of 95.3% of women in the 15- to 24-year age group, 97.5% in the 25- to 34-year group and 98% in the 35- to 45-year age group were immune to rubella. There was no statistically significant difference in the rate of rubella susceptibility between the four districts tested."

"The study is an important step in addressing the seroprevalence of rubella infection in women of childbearing age in South Africa," the authors noted.

Corcoran and his co-authors published their study in the South African Medical Journal (Seroprevalence of rubella antibodies among antenatal patients in the Western Cape. S Afr Med J, 2005;95(9):688-690).

Technologies changing the hunt for pharmaceuticals: Can African firms join the race?

Victor Konde, ATDF

Abstract

Over the last four decades, major technological advances have been made that are transforming drug and vaccines discovery, validation, delivery and production. They have also changed the way drugs are stored and distributed. This article explores some of the new developments in nanotechnology and biotechnology with a focus on the pharmaceutical sector. It also explores the technological opportunities and challenges pharmaceutical firms in Africa may face in future in keeping up or catching up with other firms and suggests ways of overcoming some of the crucial bottlenecks.

Introduction

There is a growing recognition that many diseases that afflict large populations in developing countries either have a limited number of treatment options or none at all. It is estimated that about $70 billion is spent annually on pharmaceutical research and development (R&D) globally. [1] Of this amount only about 10% goes towards diseases that affect about 90% of mankind. Millions of people in poor countries are affected by diseases for which answers (drugs, vaccines and devices) could be easy to develop if they would represent a lucrative market to warrant the high expenditure and risk associated with drug and vaccine development.

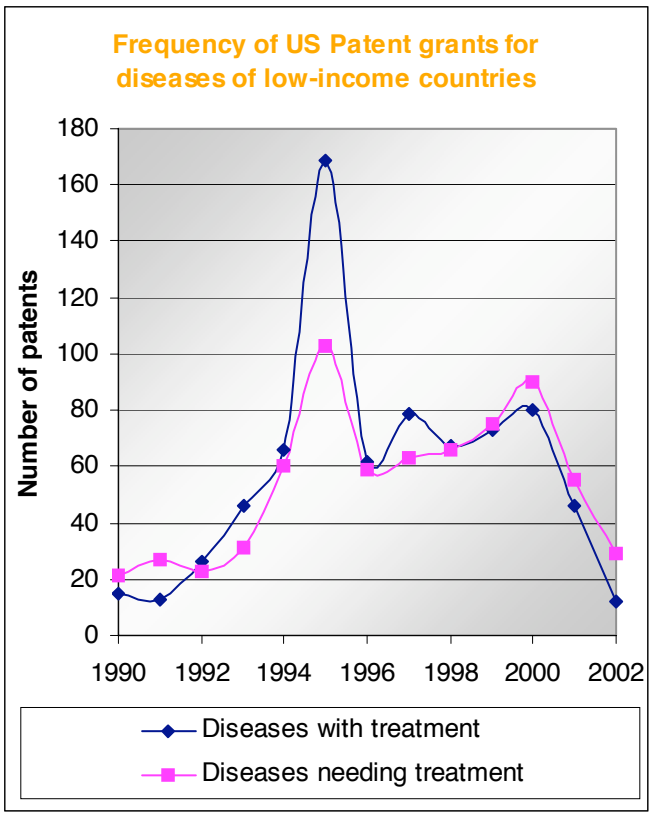
This situation is further compounded by the increases in drug-resistant parasites. For example, there are over 5,000 antibiotic substances known today with global production in excess of 30,000 tons and a total market value of $24 billion. [2]. Bacterial resistance to antibiotics has increased mainly due to increased use/abuse and similarities in antibiotic properties and structure which leads to cross resistance. This raises the cost of health care. In the USA alone, antibiotic-resistant bacteria result in about $4.5 billion extra health care expenses. In Africa, several antimalarial drugs have either been rendered useless or are about to be less useful in controlling malaria (e.g. chloroquine)

The search for completely different compounds that attack bacteria through new mechanisms such as fluoroquinolones, quinoprisitin, dalfoprisitn, linezolid, ketolides and glycylcyclines is of great interest. A number of compounds have been found in animals e.g., anti-microbial peptides, such as magnainin, which isolated from frogs. Another promising approach has been the combining of current antibiotic with compounds, called "guardian-angel", that neutralize antibiotic resistant bacteria.

A recent study revealed that the level of innovative activities that target diseases of low income countries remains low. [3] For instance, the number of patents granted, expenditure on R&D and frequency of citation in literature of diseases where 99% of the estimated burden falls in low income countries remains low.

Similarly, out of about 34 treatments approved by the US Food and Drug Administration in 2005, so far, only two target HIV/AIDS, one for meningitis and none for malaria or tuberculosis. As shown in figure 1 the number of patents grated that target diseases with a high burden falling in poor countries has, in general, increased but remained low.

The search for new drugs, vaccines and devices is a complex, long and expensive overregulated process. The development of a single product, from concept to market, could take up to 15 years and cost up to $1 billion, according to several estimates. The pharmaceu-



tical industry largely depends on a pull of knowledge bases- chemistry, biology, physiology, information technology etc- to generate, screen and validate the drug or vaccine candidates.

It is for this reason that new and emerging technologies that promise to cut down investment in R&D, reduce the time of drug/vaccine development and increase the pace of product delivery to market generate a lot of interest. New technologies also offer developing countries and their firms the opportunity to overcome market entry barriers. They provide a window of opportunity to catch up with or join the leading countries in the field of interest.

The notions of "catching up" and "leapfrogging" have partly focussed on the ability of countries to learn and become almost as good as the leading nations. [4 Although "catch-up" suggests a linear progression along the same path of development, it does not necessarily need to be viewed in a unidirectional way. Development is not a race along a fixed track where catching up is merely a question of relative speed. There are several examples of successful 'overtaking' that were largely based on running in a new direction.[5] Indeed, firms such as Genentech have emerged as leading biopharmaceutical firms by exploiting new developments in biotechnology.[1]

Leapfrogging, on the other hand, relates mainly to the speed at which catching up occurs. The notion of leapfrogging deals mainly with the ability of a country to increase the rate of catching up or to omit certain stages of technology development. New comers may not need to sequence the human genome to discover clues needed to develop treatments for diseases. The dynamic nature of the process of technological innovation means entry barriers keep changing. For example, state-of-the-art genome sequencing laboratories of the 1990 cost much less than today's sophisticated state-of-the-art genome sequencing facilities. Countries seeking to enter this race face a high-cost and lack the cumulative knowledge gained over the years by early adopters.

However, countries like Brazil demonstrated that - with a careful design and use of knowledge accumulated by others - technological leapfrogging in biotechnology is not just possible but also cost-effective. [6]. Within two years, Brazil established a virtual genome sequencing facility called ONSA and sequenced completely several genomes within budget and on-time.

2. The major technological trends

The future trends in pharmaceutical research are likely to be influenced by advances in several technological fields. These will include biotechnology and developments in information and communication technologies, materials technology, cognitive technology and nanotechnology (table 1). [7] The convergence of any of these or all of these and other fields is likely to spin-off new technologies that will make a huge impact on industrial competitiveness.

Some trends in biotechnology and nanotechnology likely to influence R&D.

Biotechnology is one field that has almost lived up to expectations. The global biotechnology industry was estimated to have generated about US$54.6 billion in revenues (compared to just US$ 8.1 billion in 1992) and employed about 184,000 persons in publicly traded firms in 2005. An estimated US$21 billion was invested in biotechnology-related research and development (R&D) activities in 2004. [8]

Most of the profits are made from health biotechnology products. It is estimated that there are some 230 biotechnology based drugs, including 13 therapeutics antibodies currently on the market, about 365 drugs in Phase III clinical trials and 55 new drug applications that were waiting for approval in the US alone.

Protein engineering or the modification of the activity of proteins is one research area of interest that is enabling firms to design and modify proteins to alter or improve their performance. For instance, Genencor is designing tumour-destroying proteins as well as proteins that will foster the immune system against viruses and cancers, just like vaccines do. Similarly, Maxygen has produced effective versions of interferons alpha and gamma, yet to be tested in people, and is developing proteins that would behave as vaccines against bowel cancer and dengue fever. Others include Viracept, a protease inhibitor for HIV (by Agouron) and Relenza™ (by Biota Holdings), an inhibitor of neuraminidase of the influenza virus

Computational chemistry and genomics, bioinformatics and structural biology are among other information tools used to analyze genomes to identify potential candidates for drug or vaccine development. With several genomes now sequenced, these tools will be needed to quickly identify potential candidates for further development- a process that could reduce time needed to discover and increase the number of potential candidate genes of interest.

The development of whole genome amplification and sequencing tools is another area that is likely to change both drug discovery and health management. In a recent announcement by the US National Human Genome Research Institute (NHGRI)- some of the emerging techniques seek to develop “Droplet-Based Digital Microfluidic Genome Sequencing" to demonstrate how existing droplet-based microfluidic electro-wetting technology can be modified to perform sequencing by synthesis reaction chemistry and "Single-Molecule DNA Sequencing with Engineered Nanopores" exploiting experience in nanopore research, protein engineering and molecular recognition, among others.[9]

However, there are other trends that will possibly influence the production and storage of drugs and vaccines. For instance, biopharming - the production of pharmacological products in genetically engineered plants or animals- is one such field. By 2003, about 300 trials of crops genetically engineered to produce various thera-

peutic products were initiated. These include modified tobacco plants that produce Interleukin-10 for the treatment of Crohn's disease, GM potatoes that produce antibodies for reducing the risk of rejection in kidney transplants, GM tobacco that produces vaccines against hepatitis B and drugs against HIV/AIDS, and potatoes that produce human insulin. Others include transgenic tomatoes containing a gene from Escherichia coli that can protect against diarrheal diseases (Lemonick, 2003). Several laboratories around the world are working on their own versions of plant-derived vaccines, using tomatoes, bananas and potatoes among other crops.

Biopharming is mainly driven by a cost advantage. For example, for medicinal products could be synthesized in plants at less than one-tenth of the cost of conventionally manufactured drugs and vaccines. By the end of the current decade, biopharmaceuticals are projected to grow into a $20 billion industry. It could ultimately bring down the cost of treating some diseases (Roosevelt, 2003).

For instance, GTC Biotherapeutics, US, has successfully engineered goats to produce 14 varieties of therapeutic protein in their milk. Creating a flock of transgenic goats costs about $100 million, a third of the cost of building a protein-production facility. In addition, when a drug maker needs to double production, the solution is to breed more animals, instead of spending $300 million on a new factory. This could decrease the cost of purified therapeutic protein from $150 to between $1-2 a gram. [10]

Nanotechnology is also changing medicine and drug discovery and production. There are about 60 drugs and drug delivery systems based on nanotechnology and about 90 nanotechnology-based medical devices that are currently being tested. Nanotechnology will greatly influence the design and nature of biosensors, biochips, drug delivery systems, bioelectronics and biomaterials. It is expected that nanotechnology market may eclipse that of biotechnology by 2010.

One area that nanotechnology is likely to make a great impact in pharmaceutical development is cellular imaging. There are several molecules in any given cell that could serve as early indicators of infection or disease. However, most standard analytical tools can not tell the movement of molecules in a cell. Scientists are developing *in-vivo* cellular imaging techniques based on “quantum dots” or qdots made of silver or gold atoms. These imaging methods allow researchers to follow the activity of a single protein molecule. In addition, they could be tagged to deliver drugs to desired parts of the body.

A team of researchers at Stanford University has developed carbon nanotubules known as "Holy Grail", about half the width of a DNA molecule, that could be used to kill cancer cells. Standard chemotherapy destroys cancer cells and normal cells thus patients often suffer numerous other side effects such as hair loss. When inserted in a tumor and then exposed to the laser, they heat up killed only the diseased cells.

Although nanotechnology offers many opportunities in the development of nanomedicine (protein and non-protein based treatment for cancers, diabetes and infectious diseases), nanodiagnostics (qdots, biosensors probes etc) and nano materials for management of burns and wounds, few firms and institutions have the capability to operate or manufacture nanoparticles. Researchers at Massachusetts Institute of Technology (MIT) have a developed a nano-printer for the mass production of nano-devices. [11] It permits individual strands of DNA to assemble themselves on a surface into original designs.

Another area is the development of tiny devices that are as sensitive and accurate as traditional bulky laboratory equipment. For example, Integrated Nanotechnologies LLC has developed a field-portable DNA analyzer (BioDetect™) to detect a host of infectious organisms, including anthrax and SARS. The analyzer is self-contained and does not require operator adjustments between tests making it easier to run. A lighter and commercial version is expected for release this year (2004). Although designed for bioterrorism in developed countries, the analyzer is a useful tool for developing countries too as it could cut down reagent needs and overcome current lack of trained personnel.

Nanotech Scientist at Purdue University announced (12th February, 2004) the development of a chip-sized version of a common detector use to identify proteins, DNA and other molecules. This could radically reduce the size of detection equipment, in a similar fashion as the move from separate transistors to integrated circuitry changed size and power of computers and similar equipment.[2]

Nanotechnology is particularly interesting as the behaviour of metals often changes at non-scale (a few atoms-wide), in a way, expanding the properties of elements. For instance, zinc oxide is normally white but is transparent at nanoscale. Such changes in properties of standard chemicals at nonoscale provide new opportunities for the pharmaceutical industry. It is estimated that $180 billion of the $1 trillion nanotechnology market will be in the pharmaceutical industry.

There are at least three major challenges that African pharmaceuticals firms may face in joining these technological revolutions. First, the level of technological sophistication needed to develop or imitate some of the innovations, especially in nanotechnology, may not be easily amassed in African firms. Second, the cost associated with technologies used in R&D may be beyond the reach of pharmaceutical firms whose budgets are no larger than a few thousands of dollars. Third, the public research institutions that are supposed to provide innovation that stimulate private sector interest may not have the required research capability.

		Biotechnology	Material technology	Nanotechnology
Biotechnology	**Computational biology** Drug testing simulations- ***Biopharma shifts; custom drugs and diagnostics***	Industry Dev, reduced cost, time and custom designed drugs	Health data on chips	Health
	Biomedical engineering *Minimally invasive surgery; artificial tissues/organs, neural prosthetics* *Health/life expectance/costs*	Lower costs/time, increased life expectancy,	Facilitating	Facilitating
Materials technology	**Tissue engineering** *Artificial heart tissue,* *Treat heart attacks with generated tissues*	Improved health	Eliminating premature deaths	
	Smart materials Personal ID/database, ***Instant secure ID/Data***	Security (biometrics)	Instant remote purchasing	Facilitating
	Agile manufacturing *Global business enterprise (consumer-direct order-deliver/maintain/track)* ***Power of business NGOs in above.***		Consumer power, Government control	
Nanotechnology	**Smart system-on-a-chip** ***Micro-locator tag with communication*** *Enabled persistence surveillance/logistics*			Industrial efficiency, Privacy barriers
	Nano-instrumentation Bio-measurements/genetic ***Timely health information***			Preventive medicine
	Molecular manufacturing Calalytic air nanoscrubber; molecular-scale for removal of CO, CO_2 at source Decrease in environmental effects of fossil fuel use			

Source: P.S. Anton et al, (2001) The global technology revolution: bio/nano/materials trends and their synergies with information technology by 2015, RAND

3. Strategies for riding the technology tide: examples from other regions.

In this section, a few examples serve to highlight the importance of utilizing technological niches, partnerships and alliances and market access. It also highlights the importance of national interest and public investment in R&D in promoting partnerships and alliances enabling firms to utilize technological niches and expand their markets.

3.1 Capitalizing on technological niches: The Korean strategy

One of the features of technological evolution is the formation of specialized market niches that utilize variants of the dominant technologies or design concepts. Technology niches are important for a number of reasons. First, they enable the lesser developed countries to enter the technology market without being required to move and compete at the frontier of its development. Second, market niches can enable significant activity by developing country firms by applying the new techniques to local problems, for which there is little interest among multinational corporations. Third, countries that are explicit about their interest in operating in specific niches are more likely to benefit from technological cooperation with larger firms in the industrialized countries. Finally, technological niches may represent an important step in the sequence of technological development.

Technology niches, especially where they are linked directly to production would involve working closely with the private sector. This would be more beneficial to emergent economies than reliance on direct support for basic research in public institutions. The appearance of technology niches, however, will place equally critical demands on the national system of innovation to provide the necessary support and inputs.

The Republic of Korean may be said to have capitalized on technological niches to develop its biotechnology industry. In 1982, a consortium of private firms formed the Korea Biotechnology Research Association (KOBRA) and soon the Government enacted the Korea Biotechnology Promotion Law and created the Korea Research Institute of Bioscience and Biotechnology (KRIBB) in 1983 and 1985, respectively.

Korea is estimated to have invested US$500 million while the private sector invested an additional US$ 1 billion in the first four years. In 2001, the Minister of Science and Technology unveiled a plan to invest about US$ 270 million to support genome research, protein chemistry and bioinformatics.

The government set aside about US$380 million to help establish another 600 biotechnology-related ventures by the end of 2003. The country also established official links and offshore centers with China and the UK for R&D. The offshore centers are setup to foster collaborative research keep local R&D centers abreast with new developments in biotechnology.

The goals of the government were clearly spelt out in the Korea Biotech 2000 Plan of Action that has three main phases and requires a total investment of US$ 15 billion by 2007. The first phase (1994-1997) aimed at acquiring and adapting bioprocessing and improving performance of R&D investment. The second phase (1998-2002) focuses on consolidation of the scientific foundation for development of novel products. The last phase (2003-2007) will target biotechnology market expansion locally and internationally.

Some of the major products of the Korean biotechnology firms include Hepatitis B vaccine that captured (40% of the market), amino acids (20% of the market) and rifamycin (10% of the market). Additionally, the country exports medical diagnostic kits, equipment and drugs. As an added incentive, researchers in government-aided institutions are allowed to establish firms to facilitate smooth transfer of technology or innovations with high tacit knowledge levels.

The biotechnology sector imported most of the enabling technologies such as those used in fermentation, vaccine and drug production to help develop the capacity need to become an exporter of drugs, vaccines and diagnostic kits. In addition, the biotechnology strategy is clearly spelt out and goal-oriented. Despite recent scandals,[3] Korea has moved from the periphery of biotechnology to a global player in stem cell research and cloning.

3.2 Market access and technology transfer: The case of Herber Biotech

Market access plays an important role in enabling firms to recoup their investment, acquire new technology and keep abreast with technological developments in other countries. International market access is particularly difficult in the pharmaceutical industry due to differences in regulatory systems. This could increase the cost of product approval and marketing. In this case, finding a partner that knows how to navigate through complex pharmaceutical regulatory regimes may be vital in gaining access to new markets.

The Cuban experiences in biotechnology commercialization highlights the important role market access plays in sustaining further product development. The Center for Genetic Engineering and Biotechnology (CIGB) has facilities that produce vaccines for meningitis B and hepatitis B. Vaccines for HIV, hemophilia and cholera are under development. In diagnostics, CIGB has produced analytical systems capable of detecting HIV, hepatitis B, herpes simplex, chagas, leprosy and other diseases. It has also produced probes for plant diseases, about 50 enzymes, and an additional 160 medical and pharmaceutical products.

However, Cuba needed to expand the market of its pharmaceutical products. To facilitate this initiative, CIGB created a semi-private enterprise, Herber Biotech. Herber Biotech has since developed joint ventures and international representatives to enable it access international markets. For examples, Kee Biogenetics, a division of Kee Pharma (India) and Heber Biotech (Cuba) have entered into a joint venture to produce and market a range of biotechnology products in India. These marketing ventures are aimed at getting access to the Indian market through special pricing and technology transfer. Similarly, the Cuban Centre of Molecular Immunology (CIM), and its commercial branch CIMAB SA and BIOCON India Ltd have finalized a joint venture agreement to set up BIOCON Pharmaceuticals Ltd, a new manufacturing facility to produce and market health care primarily in the Indian market.

Cuba recognizes that gaining access to the global market involves forging alliances with a wide range of enterprises, especially those that have extensive marketing networks. Cuba's success in biotechnology is attributed to the existence of a critical mass of scientists in natural and applied sciences as well as a political commitment to technological innovations. However, its long term growth will depend on the Cuban biotechnology industry to market it products in the global market that provide extra revenues that may be ploughed back into innovative activities to generate future products.

3.3 International alliances to facilitate technological learning: the case of Biocon India

The development of complex interlinkages involving a wide range of enterprises designed to reduce the risks associated with the development of new products shape biotechnology industry networks. These networks seek to facilitate access to and transfer of technology and information exchange, and reduce risks associated with product development, production and marketing.

There are at least four factors that promote the development of collaborations and partnerships in biotechnology: a) the multidisciplinary nature of biotechnology R&D activities; b) increasing complexity of biotechnology R&D; c) uncertainty of commercial success of biotechnology R&D products and; d) the cost of biotechnology R&D activities. [12] These factors are further compounded by growing restrictive and/or lengthy regulatory regimes or requirements that increase the cost, risk and uncertainty.

The evolution of Biocon India, a company established in 1978 in Bangalore as a joint venture between Biocon Biochemicals of Ireland and local interests, illustrates the importance of international alliances. The company

started with the production of simple fermentation products and later embarked on its own R&D programme, becoming a major player in the fields of modern biotechnology.

One of the first efforts was to develop a method of producing amylases and proteases from a carefully cooked soybean meal and roasted wheat and then sell its enzymes to Biocon Ireland. By providing a market, Biocon Ireland enabled the newly formed firm to have a steady flow of income as well as eliminating marketing costs of products.

In 1989, Biocon Ireland and its 30 per cent share in Biocon India were acquired by Unilever. Unilever's financial muscle and global standing gave Biocon new linkages and access to funds, global operating procedures, standards and financial methods. Today, Biocon India has two manufacturing plants and is one of the major Indian biotechnology suppliers of food enzymes.

CONCLUSION

Africa, like other developing regions, faces a daunting but not impossible, task in becoming a real player in the new technology-driven economy. The greatest challenge lies, firstly, in amassing sufficient human capital capable of sustaining the scientific enterprise, secondly, in creating the political will and management foresight required to harness the developing technologies and, thirdly, in having the ability to seek unique but efficient research, development, production and marketing strategies. Similarly, the legal and regulatory regimes that would promote technology development and safeguard public interest have to be setup and cultivated.

Countries such as Brazil, Cuba, India and Korea have demonstrated that new technologies could be used to build a sound technological base and develop pharmaceutical industries. The pharmaceutical industry in Africa has not received the attention it needs and deserves play a role in healthcare and wealth creation. There seems to be a belief, at least now, that Africa could rely on developed countries to develop treatments for African diseases. These will then be donated to deserving countries.

The technological opportunities and challenges presented by new developments in biotechnology and nanotechnology may require countries to take steps to invest in manpower development, institution capacity and provide incentives to industry to learn. Countries could also facilitate the formation of R&D partnerships, strategic pharmaceutical production and marketing alliances, and technology transfer through bilateral and multilateral arrangements.

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Notes

1. Genentech was formed by Robert A. Swanson (a venture capitalist) and Dr. Herbert W. Boyer (a biochemist) in 1976- the first biotechnology firm-with total operating revenue of about $4.6 billion in 2004.
2. http://news.uns.purdue.edu/html4ever/2004/040212.Sands.detector.html
3. A Seoul National University panel said the research by world-renowned Hwang Woo-suk was "intentionally fabricated http://news.bbc.co.uk/1/hi/world/asia-pacific/4554422.stm