
FROM THE FIELD

Oxymoron No More: The Potential Of Nonprofit Drug Companies To Deliver On The Promise Of Medicines For The Developing World

The oxymoron of a “nonprofit drug company” does not apply.

by **Victoria G. Hale, Katherine Woo, and Helene Levens Lipton**

ABSTRACT: Although some pharmaceutical company efforts to develop and distribute drugs in developing countries have been successful, many fall short of meeting needs in resource-poor nations. In the context of public-private partnerships, we discuss the concept of a nonprofit pharmaceutical company dedicated to developing and distributing drugs for diseases endemic in developing countries. Using the experience of the Institute for OneWorld Health, we present the vision, core elements of the product development model, and challenges confronting this model. Despite limitations, early successes raise hopes that a nonprofit drug company can exist successfully both as a global health organization and as a business.

A SERIOUS infectious disease afflicts hundreds of thousands of people, of whom thousands die in one year alone. Therapies to fight or prevent the illness are in short supply, in part because many drug companies consider investing in them difficult to justify, based on a limited return on investment. What sounds like a scenario taken from a resource-poor region actually describes the United States, which recently confronted the worst shortage of flu vaccine in its history. Such shortages in the developed world generate public outcry, but we often are unaware or unconcerned when they happen in the developing world. The flu vaccine shortage catapulted the United States into a situation confronted daily in poor countries: a lack of access to essential drugs that threatens the public health and the public purse.

Drugs represent a significant proportion of

health care expense in developing countries—accounting for 50–90 percent of out-of-pocket health spending and 25–70 percent of total health spending.¹ Access to essential medicines, defined by the World Health Organization (WHO) as treatments for deadly infectious diseases that disproportionately affect poor and marginalized populations, is far from adequate.² Fully one-third of the world’s population lacks access to essential medicines, and in the poorest regions of Africa and Asia, this figure rises to one-half.³

Access To Essential Medicines

■ **Challenges.** Providing access to needed drugs is a complex problem for resource-poor nations. Two types of problems are associated with access.

Safe and effective treatments must first exist for the disease in question—but diseases

Victoria Hale is the founder and chief executive officer of the Institute for OneWorld Health in San Francisco, California. Katherine Woo is director, Scientific Affairs, and Helene Lipton (hlipton@oneworldhealth.org) is a visiting scholar there.

that afflict primarily the poor often lack such a treatment.⁴ Between 1975 and 1999, out of 1,393 new drugs developed, only 13 (less than 1 percent) were designed to treat tropical diseases, which account for more than 90 percent of the worldwide disease burden.⁵ More broadly, only 10 percent of the US\$70 billion spent on health research worldwide each year is for research into the health problems that affect 90 percent of the world's population (the so-called 90/10 gap).⁶

Once developed, drugs must be approved by health authorities; manufactured in adequate quantities and to appropriate quality standards; priced affordably; stored properly; publicized to both providers and potential patients; and distributed to all who need them—a daunting challenge in countries with rudimentary health care delivery systems. Lapses in any step hinder access.

■ **Solutions.** Médecins sans Frontières (MSF) represents one approach to drug distribution in the developing world. Through its Campaign for Access to Essential Medicines, MSF advocates for policies to lower drug prices, encourages greater research on neglected diseases, and supports legislation that prioritizes access to medicines.⁷

Another approach is drug donation programs, whereby pharmaceutical companies provide needed medicines to people in developing countries. For example, Merck and Company has donated the drug ivermectin for the treatment of river blindness in western and central Africa for more than two decades and has helped eliminate the disease in these areas.⁸ GlaxoSmithKline (GSK) is a partner in the lymphatic filariasis elimination program, along with the World Bank, the WHO, and the United Nations Children's Fund (UNICEF).⁹ The Prevention of Mother-to-Child Transmission (PMTCT) Donations Program is a combined effort by Boehringer-Ingelheim and Abbott Laboratories to provide Viramune (nevirapine) and Determine (rapid HIV diagnostic test) free of charge to PMTCT programs involved in the prevention of mother-to-child transmission of HIV in Africa and other developing countries.¹⁰

Although donation programs have shown some success, their impact is limited because most drug companies, whose shareholders expect a return on investment, cannot be expected, by themselves, to provide drugs on the mass scale required for some diseases.¹¹ Further, many countries cannot or will not allocate funding for basic operational and logistical services to support donation programs.¹²

Developing New Drugs For Diseases Of Poverty: Growth Of Public-Private Partnerships

A number of innovative ventures, under the broad umbrella term “public-private partnerships” (PPPs) for health, have emerged to fill the gap in drugs for diseases of the poor.¹³ These partnerships among global health organizations, pharmaceutical manufacturers, biotech firms, academe, and developing-world governments have diverse organizational structures. While many support the distribution of drugs, others focus on completing the development of drugs. The latter group is sometimes referred to as product development PPPs.¹⁴

Initially, such partnerships were formed to focus on the development of a particular type of product for a specific disease. Examples include the Global Alliance for TB Drug Development, the International AIDS Vaccine Initiative (IAVI), PATH's Malaria Vaccine Initiative (MVI), and the Medicines for Malaria Venture (MMV).¹⁵ PPPs use a portfolio management approach by investing in drug development in different companies who then undertake the research. Other distinguishing features of this model include coordinated partnerships with external product developers, scientific boards with disease-specific expertise, and efficient management teams.¹⁶

Many such partnerships have engaged drug companies in drug and vaccine development efforts. For example, the MVI partnered with GSK to develop a malaria vaccine, RTS,S/AS02A, for children in Africa. A recent large Phase II clinical study, conducted in Mozambique, showed 30 percent efficacy for at least six months in 2,200 children ages 1–4

years, demonstrating “proof of principle” that a successful malaria vaccine can be developed.¹⁷ Similarly, the MMV, a company devoted to the discovery, development, and distribution of a portfolio of new antimalarial drugs via PPPs, has forged a broad basic research collaboration with GSK to identify new drug leads for malaria in the drug company’s research facility in Spain. MMV also partners with Ranbaxy (an India-based multinational drug company) to develop an antimalaria drug (OZ277/RBx11160); this partnership has recently completed Phase I clinical testing and is proceeding to Phase II in India.¹⁸ By engaging drug companies of varying sizes, PPPs advance the pace at which needed drug and vaccine therapies can be developed to combat diseases of poverty.

The Nonprofit Drug Company Model

These efforts have achieved important successes, although the unmet global disease burden remains great. To address this challenge, PPPs have continued to evolve, and additional models are now an important part of the landscape. One such model to join this community is the nonprofit pharmaceutical company, exemplified by the Institute for OneWorld Health.¹⁹ Here we highlight this model’s key characteristics.

■ **Key differentiating elements.** Operationally, a nonprofit pharmaceutical company shares the core characteristics of classic PPPs but differs from them in several ways. First, its in-house research and development (R&D) team is larger than that of classic PPPs, consisting of pharmaceutical scientists who typically perform the drug development in the absence of a pharmaceutical company. Specifically, these scientists design and implement the preclinical and clinical research protocols; analyze and interpret trial results; manage the research; prepare dossiers for regulatory approval; and actively guide the drug product through the regulatory and manufacturing processes. Second, a nonprofit drug company can tackle a wide variety of neglected diseases and can select the best development opportu-

nities available in each. Third, it is not limited in the modality of treatment: Drugs, vaccines, and diagnostics could be developed as needed.

Typically, images of pharmaceutical companies are those of big businesses with policies and decisions determined by the profit motive, while global health organizations often are depicted as publicly funded, altruistic entities, serving the needy and acting as a voice for the world’s poor. A nonprofit pharmaceutical company, where decisions to develop specific products are made based on global health needs rather than large anticipated returns on investment, represents a clear departure from the traditional pharmaceutical company model, yet it incorporates many of its organizational structures and efficiencies. Resolving the apparent oxymoron of a “nonprofit drug company” means engaging both worlds and incorporating elements of each system into a unique business model.

■ **Core components.** Several key components of the nonprofit drug company model characterize its innovative approach.

Nonprofit status. Adopting nonprofit status allows these groups to select development projects without regard to financial returns for investors. Nonprofit companies also are not handicapped by high marketing, advertising, and administrative costs.²⁰ This flexibility allows them to make efficient use of limited funds and protects them from corporate mergers or acquisitions.

Intellectual property. Nonprofit drug companies can lessen the costs of the early stages of drug development by adopting promising postdiscovery compounds that have accumulated substantial safety and efficacy data. These compounds may be licensed or donated by the pharmaceutical industry and academe, both of which produce a large number of discoveries that are never used commercially but have applications for the developing world. Savings from this recycling process optimally translate into more affordable products.

Nonprofits leverage the investment already made by drug companies and academe in three ways: (1) Off-patent drugs can be recycled for new indications. (2) Patent donations can be

used by the nonprofit company to create new drugs; such donations advance the nonprofit's mission and serve as a tax benefit for the donor organization in the form of a deduction. (3) Partnerships between a nonprofit drug company and for-profit drug companies allow a "dual-market" strategy: The nonprofit entity negotiates no- or low-royalty contracts to create drugs and takes them into the developing world, while the for-profit company uses this public investment to continue its own development in the Western market.

Affordability and pricing. Exploitation of multi-tier pricing within a developing country is an important measure to ensure the nonprofit's sustainability and the affordability of its products. Products developed by the nonprofit for the developing world could be distributed to some sectors with a revenue return (that is, wealthier markets in the developing country), thus subsidizing the no- or low-cost provision of the new therapy for the most vulnerable.

Sources of revenue. In the early stages of any such nonprofit venture, the primary source of revenue is likely to come from philanthropies. Other avenues may open as the nonprofit becomes more sophisticated in its operations. As the nonprofit begins to market its drug, its efforts could be financed, in part, by revenues from sales of marketed drugs.

Assumption of investment risk/costly activities. By assuming the financial risk for the often early and risky drug development phase, nonprofit drug companies provide incentives for for-profit companies to apply their technical expertise toward creating drugs for neglected diseases—those with anticipated minimal financial returns. Key components of these incentives are the sponsorship to seek Western regulatory approval and the preparation of a quality dossier.

Applying The Nonprofit Model

OneWorldHealth is a canonical example of how the nonprofit drug company model operates in real-world conditions.²¹ Since its inception in 2000, the company has initiated several projects that demonstrate how this model will

achieve its goal.

■ **Chagas disease.** Chagas disease is a leading cause of heart failure in Central and South America and is the leading cause of cardiovascular death among patients ages 30–50.²² Ten to twelve million people are infected with the disease-causing parasite, and at least 50,000 die each year. It is estimated that 25,000–100,000 people in the United States also are affected, mainly because of immigration.²³ There is an urgent need for new effective, nontoxic, and inexpensive treatments for Chagas disease.

As an early example of a biotech company/nonprofit drug company partnership, in February 2002 Celera Genomics provided a broad license donation to OneWorld Health for the development of the compound K-777 for the treatment of Chagas disease in the developing world. OneWorld Health scientists are conducting the necessary pharmacological and toxicological preclinical studies to reach the goal of filing an Investigational New Drug (IND) application with the FDA.

■ **Malaria.** Malaria is endemic in nearly 100 countries, and approximately 40 percent of the world's population is at risk. New strains are increasingly resistant to older, inexpensive, single drugs such as chloroquine.

In December 2004 OneWorld Health received a US\$42.6 million grant from the Bill and Melinda Gates Foundation to support a partnership with the University of California, Berkeley (UCB), and Amyris Biotechnologies, to create a synthetic supply of artemisinin, the essential component of the most effective combination treatment for malaria.²⁴ A shortage of artemisinin, caused in part by its time-consuming and labor-intensive production from the Asian wormwood plant, threatens to deprive millions of people in the developing world from receiving malaria cures. In this project, OneWorld Health will lead a three-component research plan, in which UCB will apply synthetic biology to complete development of a process to produce artemisinin from *E. coli*; Amyris will develop the process for production; and scientists at OneWorld Health will do the preclinical development and regu-

latory work to demonstrate bioequivalency between the synthetic and natural forms and secure a large-scale fermentation facility to satisfy global needs. This initiative holds promise for providing consistent, affordable supplies of artemisinin.

■ **Visceral leishmaniasis.** Visceral leishmaniasis (VL), also known as kala azar (“black fever”), is a fatal parasitic disease transmitted by sand flies. An estimated 1.5 million people worldwide are infected; the number of new VL cases per year is estimated at 500,000; and as many as 200,000 people die annually. VL kills more people than any other parasitic disease except malaria.

Patients cured of VL develop lifelong immunity, but available therapies cost as much as US\$200 and can be toxic or ineffective. OneWorld Health is developing paromomycin, an off-patent aminoglycoside antibiotic with antiparasitic properties, as a new cure for VL. Phase II trials for paromomycin were completed by the WHO’s Division of Tropical Disease Research (WHO/TDR), which then shelved the drug. In late 2004 OneWorld Health completed a large Phase III trial with support from the Gates Foundation and in collaboration with WHO/TDR. Preliminary results suggest that paromomycin is very well tolerated with high efficacy.²⁵ OneWorld Health is partnering with the International Dispensary Association, a Netherlands-based nonprofit drug supplier, to manufacture paromomycin in India and to submit it for regulatory approval first in India in 2005 and then to either the U.S. Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMA) in 2006. This collaboration ensures that the drug will be available in the developing world for about US\$10 per adult and US\$5 per child. OneWorld Health’s success in VL illustrates the potential of the nonprofit drug company model for bringing safe, effective, and affordable drugs to the developing-world market.

Implications

The preceding descriptions highlight the diverse strategies of the nonprofit drug com-

pany model with different disease targets, across geographic areas, and in various phases of development. Each project incorporates key elements of the model. First, in each case, the nonprofit plays a critical role in fostering innovative partnerships with multiple players. In developing the antimalaria compound artemisinin, for example, OneWorld Health coordinated the efforts of a major funder (the Gates Foundation), university researchers (UCB), and a start-up biotech company (Amyris).

Second, whenever possible, OneWorld Health has harnessed new technologies or previous drug development efforts to reduce drug costs. In the case of artemisinin, this meant adopting an innovative approach to producing a costly drug already in the market, albeit in short supply. For VL, OneWorld Health was able to complete clinical testing of an off-patent drug that had already been approved in numerous countries, instead of starting to develop a new drug *de novo*.

Third, the model has demonstrated its flexibility by going where the greatest unmet disease burden is and by adopting a broad and diverse portfolio that includes diseases affecting primarily poor populations (so-called single-market diseases, such as Chagas and VL), as well as diseases that are prevalent in both developing and developed countries (such as malaria and diarrheal disease).

Creative New Ventures

Nonprofit organizations targeting neglected diseases are dynamic and continue to evolve to meet global health needs. For example, the Drugs for Neglected Diseases initiative (DNDi) tackles multiple neglected diseases.²⁶ Although the Aeras Global TB Vaccine Foundation has a single-disease focus, it operates like a full-scale drug company, with internal research teams, multiple antigen targets, and manufacturing capabilities.²⁷ Surely, there will be other permutations as this dynamic field continues to mature. Regardless of the configuration, all actors in this sector face similar challenges.

Challenges Ahead

■ **Making the transition to a financially self-sustaining model.** The nonprofit enterprise in this area initially is highly dependent on philanthropic funders, who are understandably reluctant to fund programs indefinitely. Given the high cost of developing a drug and bringing it to market, finding ways to become financially self-sustaining without compromising the organization's core mission is a key challenge. Solutions might lie in creative social entrepreneurship. C.K. Prahalad has argued that the four billion people living on less than two dollars per day represent a vast, untapped market.²⁸ Using tiered pricing or a sliding scale reduces risk to the nonprofit and allows for multiple funding streams, as philanthropic dollars are combined with local revenues.

■ **Engaging the drug industry.** Partnerships with the drug industry are vital for reaching a critical mass of stakeholders capable of developing, marketing, and distributing drugs and vaccines in the developing world; industry should not be expected to shoulder the entire burden. The for-profit pharmaceutical industry is driven by its responsibility to guarantee a return on investment for its shareholders. Fear of the "backflow" of cheap drugs from the developing world to wealthier markets, where the company may have a competing product for which it could already command a high price, could deter potential industry partners.

Even when partnerships are established, challenges remain. For example, some companies might donate intellectual property for compounds that no longer have an active product team. Under such circumstances, the nonprofit might have a more difficult time assuring the speedy development of the drug.

■ **Sustaining the supply of affordable medicines.** A nonprofit drug company confronts the challenge of creating drugs that are inexpensive both to manufacture and to market. In addition to the limits this requirement places on treatment modalities that may be used (for example, biologics are often too expensive), it places severe constraints on the

costs of production. Manufacturing will most likely occur in endemic countries, where incentives may be necessary to maintain local production of drugs with razor-thin margins. It also is possible that manufacturing will occur through partnerships between nonprofits and large pharmaceutical companies. Innovation at all levels is essential.

■ **Distribution.** No matter how many drugs or vaccines are developed, product development organizations will be unable to deliver them to some patients in need. The lack of an adequate public health infrastructure challenges even the most organized groups. Should the organization choose projects where a distribution system is in place? Or should it assume the challenge of developing a system? Nonprofits will have to evaluate carefully their choices early in the development process.

IN THE RECENT U.S. flu vaccine shortage, the country experienced, in a very limited way, the overwhelming barriers to accessing medicines in the developing world. Challenging the dominant acceptance of global health inequities and promoting the right to health of the marginalized and poor of the world are basic tenets upon which the emerging nonprofit drug company sector is based. Despite the challenges that remain, this innovative model for drug and vaccine development raises hopes that a nonprofit drug company can exist successfully, both as a global health organization and as a business.

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NOTES

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