

Good Medicine: Encouraging Neglected Disease Research

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Discoveries in the treatment and prevention of disease through the use of drugs and vaccines have increased average life expectancy, yet no effective vaccine exists for diseases such as tuberculosis, and no vaccines have been developed for HIV/AIDS and malaria, resulting in five million deaths annually. The eighth Millennium Development Goal (MDG) encourages global Public Private Partnerships to facilitate the development of drugs for AIDS, malaria, TB and other neglected diseases. Partnerships and incentives have been effective in inducing multinational pharmaceutical companies back to neglected disease research by ensuring market demand for the drugs, by providing downstream access that has 'pulled' the drugs into markets, and by demonstrating corporate social responsibility that has garnered positive publicity.

Introduction

Developments in the pharmaceutical industry have been a critical factor in improving quality of life and longevity. Studies have demonstrated that discoveries in the treatment of infection through the use of drugs, as well as the prevention of disease through the use of vaccines, have increased life expectancy in developed nations from 47 years in 1900 to 77 years in 2000 (ElderWeb, 2008). Studies have also demonstrated, however, that few vaccines and drugs have been developed to prevent and treat diseases that primarily affect the poorest nations. Between 1975 and 1999, only 13 new neglected disease drugs had been developed (Moran, Ropars, Guzman, Diaz & Garrison, 2005). Vaccinations for diseases such as tuberculosis (TB), HIV/AIDS, and malaria have not been developed, and uptake of drug treatments for disease is delayed by as much as 10 to 15 years after their introduction into developed countries due to cost and delivery issues (Center for Global Development [CGD], 2005).

The Global Forum for Health Research (2004) found that less than 10 percent of global health research and development resources are dedicated to diseases specific to poor countries because of the small profit margin for drugs primarily used in those countries. In human terms, however, these diseases affect 90 percent of the world's population and kill five million people each year (CGD, 2005). The discrepancy observed between the importance of these diseases and the amount of resources dedicated to them is known as the 10/90 gap. However, there has been recent significant debate regarding the best ways to encourage pharmaceutical companies to develop vaccines and drug treatments for the prevention and treatment of rare diseases and disease strains that primarily affect poor countries, known collectively as "neglected diseases" (Kremer, 2002).

Against this stark backdrop, the United Nations General Assembly issued its Millennium Declaration in 2000, which established eight goals to be measured and attained by the year 2015 related to alleviating human

suffering and encouraging human development. The eighth Millennium Development Goal (MDG) encourages global partnerships to "in co-operation with pharmaceutical companies, provide access to affordable essential drugs in developing countries" (United Nations General Assembly, 2000). To achieve this goal, the Group of Eight countries—Canada, France, Germany, Italy, Japan, Russia, the United Kingdom, the United States, and European Union—support MDGs by "increasing direct investments... through such mechanisms as Public Private Partnerships... to encourage the development of ... drugs for AIDS, malaria, TB and other neglected diseases" (Moran, 2005). In addition, the Finance Ministers of the G7 nations support creating incentives to encourage the development of vaccines and drugs to prevent and treat neglected diseases for which there is not a large enough market to attract private sector investment in research and development (G7, 2005).

There has been vigorous debate on how to structure incentives to encourage multinational pharmaceutical companies (MPCs) to undertake neglected disease research. According to the Initiative on Public-Private Partnership for Health (2003), global health partnerships (GHPs) have contributed to the participation of pharmaceutical companies in public health issues and have created effective partnerships, particularly in the areas of project and product management skills.

Closing the 10/90 Gap

Since 2000, four of the top twelve MPCs have dedicated neglected disease research and development units and three others have undertaken research on a smaller scale. MPCs conduct nearly one-half of the 60 neglected drug research projects currently in progress (Moran, 2005), with most of the research being conducted by four companies: GlaxoSmithKline,

Novartis, AstraZeneca and Sanofi-Aventis (see Appendix 1).

MPCs assess pharmaceutical research holistically – seeking to offset the high cost to develop neglected disease drugs against the broad range of incentives that are available, as well as assessing the intangible value of the positive publicity of neglected disease research (Moran, 2005). The incentives and positive publicity offered by partnering with GHPs have tipped the scale of feasibility of neglected disease research for MPCs, and more are undertaking neglected disease research today than were in 2000. As a result, these companies now conduct half of new neglected-disease drug development activity working with GHPs or alone, but usually with a view to subsequent partnering with GHPs (Moran, 2005).

It is important to highlight that this activity has been initiated in the absence of significant new government incentives. Eighty percent of GHP drug development activity is funded through private philanthropic organizations, while the industry institutes are largely self-funding, although sometimes with GHP project funding input (Moran, 2005).

Pursuant to MDG 8, there has been a recent proliferation of GHPs, which have been established to address global health issues and serve as an important donor for research on the prevention and treatment of neglected diseases (Buse & Harmer, 2007). GHPs are comprised of non-profit foundations, and public and private institutions. In addition to offering financial inducements for research, many GHPs actively promote downstream access and healthcare capacity building, which will “pull” new developments into the market (Grace, 2006). These activities ensure that developed drugs have a more predictable and sustainable market, which is critical to MPC’s assessment of market attractiveness of a drug.

GHPs like the Global Alliance for Vaccines and Immunizations (GAVI), Institute for One World Health (iOWH), Medicines for Malaria Venture (MMV), International AIDS Vaccine Initiative (IAVI), and the Global Fund to Fight AIDS, TB and Malaria (Global Fund) have raised the visibility and importance of certain diseases on political agendas through brand-building and public relations (Grace, 2006). GHPs are funded by philanthropic organizations like the Gates Foundation, which has contributed at least \$1 billion to 11 GHPs and \$150 million alone to the Global Fund for the development of the vaccines for HIV/AIDS, TB and malaria (Grace, 2006).

As of December 2004, MMV, the TB Alliance, Drugs for Neglected Diseases and iOWH reported 47 neglected disease drug research projects, with 18 drugs in clinical trials, two in registration and eight to nine drugs expected to be released by 2010 (Moran, 2005). This compares to 16 new neglected disease drug projects being undertaken solely by pharmaceutical

companies (Moran, 2005). Collectively, GHPs reported eight diagnostics, 25 drugs, eight microbicides and 50 vaccines in development for diseases that primarily affect poor countries (Grabowski, 2005).

Drivers of MPC Activity

MPCs have begun to participate in neglected disease research for two reasons: the ability to avoid losses when undertaking the development of low margin drugs, and the increased visibility and positive publicity from undertaking GHP-sponsored, high profile development of neglected disease drugs.

Changes in Business Models

The pharmaceutical industry is characterized as high risk and high reward, with long and expensive development cycles that frequently end in failure. Typically, a fraction of one percent of the new chemical entities (NCEs) that are synthesized and examined in pre-clinical research end in human testing (Pharmaceutical Research and Manufacturers of America, 2003). To obtain approval for one drug from the Food and Drug Administration (FDA), a firm generally screens 5,000 to 10,000 NCEs. Of these, 250 NCEs are tested in pre-clinical settings; five make it to clinical testing; and one ultimately receives approval from the FDA (CGD, 2005). The average length of time from early stage discovery of an NCE to FDA approval to market has been as much as 7 to 20 years (CGD, 2005), at a cost range between \$400 million to \$1 billion in 2000 dollars (Grabowski, 2005) and an average development cost of \$802 million (CGD, 2005) for drugs recently introduced in the United States. Most companies typically seek a peak sales threshold for drug candidates at \$500 million per year or more in order to recapture development costs and reinvest in building the research pipeline (Moran, 2005).

The business case for the development of vaccines is weaker than the one for the development of drugs. Because vaccine research is less profitable, industry analysts speculate that the lack of profitability was responsible for the decline in vaccine manufacture in the U.S. from ten licensed manufacturers in 1980 to five remaining in 1992 (Walt & Buse, 2006). The total market size for vaccines globally and in developing countries is approximately \$6 billion and \$400 million per year, respectively (CGD, 2005) whereas the worldwide pharmaceutical market is valued at \$680 billion annually (Walt & Buse, 2006). While the demand for vaccines and drugs for developing countries is high, poor countries are accustomed to buying vaccines at “pennies per dose” (CGD, 2005) and this pricing structure does not allow pharmaceutical companies to recover research and development costs. Because of the significant risk and investment related to drug development, pharmaceutical firms have focused

development efforts and research funding towards products likely to produce the greatest commercial return (CGD, 2005). Drugs for diseases affecting developed nations have more predictable market demand and developed countries have the financial resources to purchase newly introduced drugs.

According to Moran (2005), after the establishment of the MDGs in 2000, significant structural changes occurred in the pharmaceutical industry and the public sector that positively affected MPC's motivations for and evaluation of undertaking neglected disease research. The industry underwent a shift from taking a "start to finish" approach to drug development (i.e., managing the development cycle from the discovery of the NCE to the registration of the product) to efforts focused solely on particular segments of the research pipeline. This shift was caused by deep-seated structural changes in the industry, particularly the formation of new pharmaceutical industry neglected-disease institutes—now employing over 200 scientists—and the creation of new drug development GHPs, which now conduct three-quarters of all identified neglected-disease drug development, sometimes in partnership with these industry institutes (Moran, 2005). Proponents of this view state that MPCs now are relying heavily on outside partners, such as GHPs, small and/or developing country pharmaceutical companies, or government-sponsored research institutions, to support both early stage research as well as expensive late stage clinical development activities such as accessing technical and scientific expertise in neglected diseases; obtaining suitable developing country clinical trial populations and support; and securing regulatory and distribution commitments from developing country governments (Moran, 2005). This change in business practice has significantly lowered development costs, and has allowed MPCs to move from a purely commercial business model (recovery of all research and development costs) to a "no-profit, no-loss" model of development. According to Moran (2005), in the "no-profit, no-loss" model, MPCs undertake neglected disease research by lowering their research costs to a minimum (no loss), so that they may, in turn, sell the products at low or no markup (no profit). The no profit, no loss model aligns with the mandate of GHPs and their incentive programs.

The Advent of Corporate Social Responsibility

Moran (2005) posits that because public attention to global health disparities are at an all time high, significant resources have been committed to combat disease and to develop new products. Her interviews with MPC officials indicate that non-commercial factors such as corporate social responsibility and positive public relations also drive them to participate in neglected disease research. In the absence of incentive programs, neglected disease drugs have been developed

through the philanthropic programs of several MPCs. Merck developed and donates Mectizan for the treatment of river blindness, and provides infrastructure support for its delivery to 200 million people in 33 countries. GlaxoSmithKline, Novartis, and Pfizer have also developed and donated drugs for the treatment of filariasis, leprosy and anti-trachoma, respectively.

While the majority of top twelve MPCs participate in neglected disease research, it is unclear whether incentives will be successful in enticing MPCs that have abandoned the neglected disease research back into the market. Leaders from MPCs that do not participate in neglected disease research were quoted by the Center for Global Development (2005) as saying, "I wish you could make the government understand this... the company has to have decided to go in for other reasons" and "Neither cash nor good PR are going to be enough to drive us back into structured neglected disease R&D" (Moran, 2005). Other non-participant companies indicated that they were wary of publicizing in house leads for neglected diseases, because "knowledge [of] that discovery inevitably meant pressure on a company to sign up for the expensive job of bringing that product to registration and distribution" (Moran, 2005). While incentives may not induce MPCs which have made the business decision to abandon neglected disease research back to the market, most of the top 12 MPCs are very actively participating in partnerships and seeking incentives.

Incentive Models

There are two primary incentive models used to stimulate research on vaccines and drugs – push and pull incentive programs. Push programs work to lower the costs of development mainly through research partnerships, tax incentives, research grants, or expedited regulatory review. Pull programs focus on enhancing revenue through market-based mechanisms like advanced market commitments, longer periods of market exclusivity, and transferable rights of market exclusivity to higher margin products (Grace, 2006).

The distinction between push and pull incentive programs is who funds the research and who bears the risk of development failures. With push incentives, donors fund the research and bear the risk of failure during development. All industry players are interested in push incentives because it mitigates the risk associated with undertaking research. With pull incentives, industry funds the research and bears the risk of failure during development. Companies only obtain the incentive if they are successful in developing the drug or vaccine (Grace, 2006). Therefore, only large industry players (MPCs) and smaller players with excellent connections to financial capital will be able to sustain the cost of funding research and bear losses under pull incentive models. Small firms without access

to capital may be able to respond to pull incentive programs if they are coupled with interim push funding (Grace, 2006).

Push incentive programs have existed for several years and evidence suggests that they are effective in inducing MPCs to undertake neglected disease research. Push incentives not only fund speculative research, but also serve as a market signal that the “pull” for the technology is coming (Grace, 2006). On average, 44 percent of pharmaceutical research funding is provided by governments through institutions like the U.S. National Institutes of Health and the United Kingdom Medical Research Council. Eight percent of research funding is from non-profit and foundation sources and 48 percent of funding is from industry (Grace, 2006). The most notable push funded project is the development of the malaria vaccine fully funded through licensure by the Bill and Melinda Gates Foundation. The most likely first candidate to market is a MPC, GlaxoSmithKline (GSK), with an anticipated product market introduction in 2011 (Grace, 2006).

Kremer and Glennerster (2004) differentiated between push and pull programs by writing that push programs reward input and pull programs reward output. They wrote that one of the consequences of push programs rewarding input is that that research fund allocation decisions are made before the product is created and its efficacy can be proven. Often project managers and investigators have significant financial interests receiving grants for their research, which is an incentive for them to make overenthusiastic predictions about their products’ potential.

One of the most egregious examples of a push program failure took place at USAID in the 1980s. The malaria vaccine project director, James Erickson, exaggerated the potential of a vaccine research team’s results to obtain a \$2.8 million grant. The project’s principal investigator then transferred grant funds to his personal account. In a separate scandal, Erickson received a kickback for arranging a contract with an associate to obtain malaria test monkeys. He eventually pleaded guilty to making false statements, filing false tax returns, and accepting illegal gratuity. USAID spent more than \$60 million on malaria vaccine research by 1986, but it still does not have a vaccine (Kremer & Glennerster, 2004).

Pull incentive programs, for example Advanced Market Commitments (AMCs), are a recent development and consequently, there is little empirical data regarding their effectiveness in inducing MPCs to undertake neglected disease research. AMCs provide developers with contractual price and volume guarantees in exchange for guaranteed supply or compulsory licensing upon the release of the new pharmaceutical (Grace, 2006).

Preliminary research on pull incentives indicates that the size of the incentive affects the pharmaceutical

industry’s behavior, at least in circumstances where there is a commercial market for the product. One study found that pharmaceutical research spending was strongly influenced by the size of the market, and an increase of one percent in market size resulted in a four to six percent increase in the number of new drugs in that category (Grace, 2006). Currently, AMCs are proposed to fund research only on the development of vaccines for diseases like TB, HIV/AIDS and malaria, and the majority of candidates for the first pilot AMC for pneumococcal disease are MPCs: Wyeth, GSK, Merck, and Aventis (Grace, 2006).

Kremer and Glennerster (2004) advocate for a combination of pull and push programs to encourage manufacturers to provide vaccinations for low-income countries, but they argue that there is no pull system in place for diseases that primarily affect low-income countries and explore ways of creating an appropriate pull system. They argue that donors should create markets for low-income countries by entering into long-term contracts with vaccine manufacturers in which the donor agrees to pay a lump sum for vaccinations. The donor could then buy vaccinations at a relatively high cost to provide the promised funds, and then pay the manufacturer to provide the vaccinations to low-income countries at a price slightly greater than production cost. Another potential pull program would be for donors to hold a competition that would reward a significant sum to the first manufacturer who produced a vaccine appropriate for low-income countries.

According to Kremer and Glennerster (2004), a key advantage of pull programs is that they reward results, allowing donors to avoid losing money to research that does not deliver. They do warn, however, that the product specifications and eligibility requirements should be narrowly tailored to meet the satisfaction of the products’ users. In 1992, two dozen American electricity utilities created the Super Efficient Refrigerator Program (SERP), which would reward millions of dollars to the first manufacturer to develop an energy-efficient refrigerator that met its specifications. The winning unit cut energy costs by 40 percent, but it cost \$1,400 and came in an unpopular side-by-side style. It sold poorly and was discontinued.

The combined use of push and pull incentives, for example the U.S. Orphan Drug Act (ODA), has also been highly effective in stimulating rare disease research (defined as those diseases that affect less than 200,000 in the U.S.). The orphan drug market has an annual value of \$103 million per year (Moran, 2005). Because rare diseases have small markets and uncertain demand, MPCs are unwilling to invest to develop orphan drugs for the treatment of rare diseases, opting instead to invest in treatments for prevalent diseases with high expected returns (Rin-laures & Janofsky, 1991). In the 20 years before the ODA was enacted, only 10 drugs had been developed and approved for use for rare

diseases. The ODA, enacted in the U.S. in 1983, was a response to the lack of innovation for diseases that are considered rare. The ODA provided several incentives to pharmaceutical firms to develop drugs to treat rare diseases: expedited regulatory review and approval, abbreviated clinical trials, 50% tax credit on all research and development expenditures, and a 7 year market exclusivity provision – the most attractive of all incentives to MPCs under the Act (Rin-laures & Janofsky, 1991).

By 1990, 45 orphan drugs had been approved for use and another 133 were in abbreviated clinical trials (Rin-laures & Janofsky, 1991). Some policymakers are recommending amending the ODA to include neglected diseases in developing countries. However, it is important to note that the ODA has succeeded because, in addition to tax incentives and government grants, MPCs can recoup costs by charging high prices for the drugs. One example is the drug Ceredase, used to treat Gaucher's disease, which costs hundreds of thousands of dollars per year of treatment. Since purchasing power of developing nations is limited, the orphan drug mechanism alone is not likely to work (Medecins Sans Frontieres, 2001). The pharmaceutical industry, however, recently proposed the Tropical Disease Drug Act, which, like the ODA, would combine push and pull incentives to stimulate research on tropical diseases. Several incentive programs relevant to MDGs are currently being offered to encourage pharmaceutical companies to partner with universities, not-for-profit organizations and research institutions. Some relate to the treatment and prevention of neglected diseases (see Appendix 1).

Notable Incentive Programs

GHPs primarily use push incentives in the form of research grants to encourage neglected disease research (Grace, 2006). The Gates Foundation recently announced its “Grand Challenges Exploration” which will provide \$100 million in grant money to help scientists across the globe pursue research related to latency in TB, a prevention or cure for HIV/AIDS, as well as other neglected global health issues. This initiative is an expansion of its “Grand Challenges in Global Health”, which was launched in 2003 in partnership with NIH. Grand Challenges Explorations will foster early-stage innovation in global health research and expand the pipeline of ideas that merit further exploration (Grant Challenges in Global Health, 2008)

The first large pull incentive demonstration project was recently announced. GAVI, as well as an alliance of international donors, including Italy, United Kingdom, Canada, Russia, Norway and the Bill and Melinda Gates Foundation, launched the first pilot AMC in the amount of \$1.5 billion for the development of a

vaccine for pneumococcal disease. It is estimated that 5.4 million child deaths can be prevented by 2030, and that 30 of the 72 eligible GAVI countries indicated interest to use the pneumococcal conjugate by 2010 (PneumoADIP, 2008). GAVI is encouraging multiple developers, and particularly those manufacturers from emerging countries. Currently one licensed vaccine exists, Prevnar, which is manufactured by Wyeth, and 20 candidates are in the research pipeline, developed primarily by MPCs like GSK, Merck, and Aventis. It is anticipated that the first payments will begin to developers in 2009 and will continue through 2020 (Moran, 2005). AMCs are proposed to encourage HIV/AIDS, tuberculosis, and malaria vaccine development.

Additional Considerations

Moran (2005) also noted that small pharmaceutical companies (SPCs), including most contract research organizations, are important research partners to MPCs who engage in neglected disease research. SPCs do not view neglected disease drugs as no profit/no loss products, but instead seek to maximize the commercial potential of these markets through licensing out technology to MPCs as well as direct sales (Moran, 2005). Moran interviewed a spokesman for Zentaris, the developer of the new anti-leishmaniasis drug, miltefosine, who noted, “while such a market would be negligible for a big pharmaceutical company, it has a good economic scale for us” (Moran, 2005).

The relationship between MPCs and SPCs is symbiotic. SPCs fulfill a critical role in neglected disease research – keeping the MPC pipeline supplied with new technologies. Around half of the 63 ongoing neglected disease projects are being conducted by SPCs (Moran, 2005) and as much as 60 percent of the clinical stage pipeline in MPCs originated from SPCs through licensure or acquisition (Grace, 2006). MPCs, therefore, serve as an important conduit of funding to SPCs that enable them to undertake risky pharmaceutical research. GHP incentives have provided funding to MPCs, which, in turn, partner with SPCs to undertake neglected disease research.

Because of the important role SPCs play in neglected disease research, it is important that incentive models also consider the unique financial constraints of SPCs. Mills and Livingston (2005) found that SPCs were acutely concerned with the funding gap, termed “the Valley of Death,” between early development of a drug, which can be supported by public research grants (push incentives), and proof of concept, which attracts MPC investors. Traversing the Valley of Death requires public and private investment. Interviewees indicated that pull incentive programs like AMCs which reward only successful candidates are attractive but they do not address this funding gap. The study recommends that AMCs provide interim milestone payments or combine

push incentives like grant funding with pull incentives to bridge the Valley of Death (Grace, 2006).

Summary

The advent of GHPs and incentive programs directed at encouraging neglected disease research has increased MPC activity in this sector of the pharmaceutical industry. Incentives have been highly effective at encouraging MPC participation in neglected disease research—seven of the top 12 MPCs are undertaking one-half of all neglected disease research and are providing the groundbreaking developments in neglected disease drugs and vaccines. It is unclear whether incentives are effective in inducing MPCs who have left neglected disease research to return to it.

Policymakers creating incentive programs must view incentive programs holistically as pharmaceutical companies do. Because of the risk associated with drug development and the poor, the standalone business case for neglected disease research is weak. MPCs and SPCs do not evaluate incentives individually, but instead look at a comprehensive picture of risks and rewards in the development of drugs (CGD, 2005). The combination of push and pull incentive programs, as well as consideration of the positive publicity associated with neglected disease research, is essential to encourage a broad range of market players to undertake research as well as to continue to innovate on existing drugs. Crafting incentive programs that address the financial needs of both MPCs and SPCs will accelerate the development of drugs and vaccines, as well as encourage multiple players and stimulate innovation (Advance Market Commitments for Vaccines website, 2008). Current and proposed AMCs account for and assume certain levels of push funding (Grace, 2006). Creating mechanisms to make neglected drug research more feasible for SPCs will allow SPCs to continue to provide novel technologies to MPCs and eventually to the market.

MPCs are also motivated to undertake neglected disease research as a corporate social responsibility activity, and they seek positive publicity from participating in neglected disease research. Firm commitments to provide continued financial support from the United Nations, G8 nations and other organizations will enhance the sustainability of the most effective GHPs and will increase the credibility of the commitments so that MPCs will get the positive public visibility they seek (CGD, 2005).

Finally, ensuring that neglected disease drugs have a predictable market demand is critical as market size is a decisive factor in MPCs' and SPCs' decisions to participate in neglected disease research. An increase of one percent of market share for a drug will result in a four to six percent increase of research activity in the drug category (Walt & Buse, 2006). Partnerships with

GHPs which undertake significant downstream access activities help to “pull” drugs into the market and are particularly appealing. Improving the speed and efficiency with which drugs are approved and delivered to market is important to MPC and SPCs' analysis of market size. Partnerships with GHPs that provide access to clinical trial populations in developing countries and can forge relationships between MPCs and the regulatory agencies of local governments are also desirable. GHPs should be encouraged to identify and adopt best practices in their relationships with the public sector, particularly as it relates to increasing the efficiency in dealing with the procurement and delivery systems of developing countries (Buse & Harmer, 2007).

The WHO (2004) suggests a comprehensive policy reform model designed to improve outcomes for the poor (see Appendix 2). The paradigm has three tenets: increasing predictability of external funding and coordination with partners; making health central in the countries' macroeconomic frameworks and increasing internal allocation of resources to health; and improving effectiveness of health delivery systems and monitoring outcomes. GHPs and their donor funding figure prominently in all three targeted areas. Coordinating GHPs and other external partners' activities and aligning those activities and funding with national health priorities are essential, but beyond the scope of this paper. This coordination would enhance MPCs' abilities to develop and deliver products targeted to the needs of the population.

Global health partnerships (GHPs) and their multilateral donors provide incentives to induce MPC participation in research that affects the poorest populations. These incentives have increased MPC participation in neglected disease research. MPCs bring a wealth of experience to neglected disease research by supporting the chain of innovation that includes public and smaller private players. The partnership of MPCs and GHPs have tremendous promise to facilitate better health outcomes and longer lives for the millions of people vulnerable to neglected diseases.

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Appendix 1

Multinational pharmaceutical companies and public-private partnerships (PPPs) to improve health in the developing world.

HIV/AIDS – Antiretroviral Access PPPs

Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck & Co., Inc. and Roche

HIV/AIDS – Mother & Child Programs PPPs

Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Johnson & Johnson, Novartis and Roche

HIV/AIDS – Capacity Building PPPs

Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Johnson & Johnson, Japan Pharmaceutical Manufacturers' Association, Merck & Co., Inc., Pfizer and Roche

HIV/AIDS – R&D PPPs

Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., Novartis and Sanofi-Aventis

Malaria – Access & Capacity Building PPPs

GlaxoSmithKline, Novartis, Pfizer and Sanofi-Aventis

Malaria – R&D PPPs

GlaxoSmithKline, Novartis, Sanofi-Aventis and Sigma-Tau

Tuberculosis – Access & Capacity Building PPPs

AstraZeneca, Eli Lilly, GlaxoSmithKline, Novartis and Sanofi-Aventis

Tuberculosis – R&D PPPs

AstraZeneca, Bayer HealthCare, GlaxoSmithKline, Novartis and Sanofi-Aventis

Tropical Diseases – Eradication or Elimination Programs PPPs

Bayer HealthCare (sleeping sickness), GlaxoSmithKline (lymphatic filariasis), Johnson & Johnson (Guinea worm), Merck & Co., Inc. (lymphatic filariasis, onchocerciasis), Novartis (leprosy), Pfizer (trachoma) and Sanofi-Aventis (sleeping sickness)

Tropical Diseases – Access, Capacity Building PPPs

Bayer HealthCare, Gilead, Johnson & Johnson, Merck KGaA, Sanofi-Aventis and Schering-Plough

Tropical Diseases – R&D PPPs

GlaxoSmithKline, Novartis, Pfizer, Schering-Plough and Wyeth

Vaccine-Preventable Diseases – Access & Capacity Building PPPs

Bayer HealthCare, Crucell, GlaxoSmithKline, Merck & Co., Inc., Novartis, Sanofi-Aventis and Wyeth

Vaccine-Preventable Diseases – R&D PPPs

GlaxoSmithKline, IFPMA Influenza Vaccine Supply ITF, Merck, Inc., Novartis, Sanofi-Aventis and Wyeth

Child & Maternal Health PPPs

Abbott, AstraZeneca, Bayer HealthCare, GlaxoSmithKline and Johnson & Johnson

Chronic Diseases PPPs

Abbott, AstraZeneca, Novartis, Novo Nordisk and Sanofi-Aventis

Source: International Federation of Pharmaceutical Manufacturers and Associations (2008)

Appendix 2

Key push and pull mechanisms relevant to MDG 8.

Push Mechanisms

- A range of instruments used by the US FDA to promote drug development, such as patent extensions to encourage licensing of drugs in children, tax incentives to promote development of drugs granted orphan status (for drugs with US market size <200,000 patients), and fast-track options for approving drugs in areas of unmet medical need (<http://www.fda.gov>).
- The UK Department of Health's Medicines for Children Initiative, which provides financial support to research networks for developing pediatric drugs.
- The WHO Special Programme for Research and Training in Tropical Diseases (WHO-TDR), established in 1970, is a partnership of four cosponsors, 22 WHO member states, and 12 foundations and agencies with annual funds of US\$30 million (<http://www.who.int/tdr/index.html>).
- The Medicines for Malaria Venture, founded in 1999, has attracted US\$263 million from donors (<http://www.mmv.org>).
- The TB Alliance, founded in 2000, has attracted US\$193 million in funding (<http://www.tballiance.org>).
- The Institute for OneWorld Health founded in 2000, a US-based non-profit pharmaceutical company (<http://www.oneworldhealth.org>).
- The Drugs for Neglected Diseases Initiative founded in 2003 by five public-sector research organisations, Médecins Sans Frontières, and WHO-TDR (<http://www.dndi.org>).
- The GAVI Alliance, a global PPPDP, which supports R&D and access to vaccines for children in developing countries (<http://www.gavialliance.org>).
- The International AIDS Vaccine Initiative (<http://www.iavi.org>), a global PPPDP, which supports R&D to develop AIDS vaccines.

Pull Mechanisms

- 2007 EU Regulations on Paediatric Medicines, which provide for market exclusivity extensions for drugs designed for paediatrics (<http://www.mhra.gov.uk>).
- Supplementary protection certificates in Europe provide patent extensions (once the corresponding patent expires) of up to five years for drugs with a new ingredient, to compensate for regulatory delays during development and approval stages.
- Advanced market commitments, aimed at creating a market for future vaccines to stimulate private investment in vaccine R&D and manufacturing capacity, are legally binding commitments to purchase at an agreed price vaccines once developed that primarily address diseases of resource-poor countries. This is financed through the International Finance Facility for Immunisation, a multilateral organisation supported by several sovereign donors to the tune of US\$4 billion.
- The Global Fund to Fight AIDS, Tuberculosis and Malaria, which since 2001 has committed US\$7.1 billion in 136 countries (in part for drug purchase to control these diseases) (<http://www.theglobalfund.org>).
- PEPFAR (US President's Emergency Plan for AIDS Relief), which by September 2006 had provided US\$819 million for purchase of antiretroviral drugs for HIV (<http://www.pepfar.gov>).
- UNITAID uses airline taxes to create a market for missing essential medicines, such as paediatric medicines for HIV/AIDS and second-line medicines for tuberculosis and malaria (<http://www.unitaid.eu/en>).
- Social policy bonds, defined as "non-interest bearing bonds, redeemable for a fixed sum only when a targeted social objective has been achieved", could be an alternative to advance market mechanisms, and could be used to signal substantial incentives for success in achieving a social policy goal of developing an effective obstetric drug and using it to reduce maternal or perinatal mortality in a particular setting

Source: Fisk & Atun (2008)