

Ending the R&D Crisis in Public Health:

Promoting pro-poor medical innovation

Diseases that disproportionately affect the developing world cause immense suffering and ill health. Medical innovation has the potential to deliver new medicines, vaccines, and diagnostics to overcome these diseases, yet few treatments have emerged. Current efforts to resolve the crisis are inadequate: financing for research and development (R&D) is insufficient, uncoordinated, and mostly tied to the system of intellectual property rights. Delivering appropriate medicines and vaccines requires reforms to the existing R&D system and a willingness to invest in promising new approaches.

Summary

Insufficient resources are dedicated to developing the new vaccines, diagnostics, and medicines that can address health needs in developing countries. Less than ten percent of global health research spending is dedicated to diseases that primarily afflict the poorest ninety percent of the world's population: the '10/90 gap'. The lack of appropriate medicines to prevent and treat the causes of mortality and morbidity in developing countries has dramatic consequences. Neglected tropical diseases kill 500,000 people every year. Diseases that are controlled in the rich world, such as tuberculosis, cause up to 2 million deaths annually. Existing medicines are often inappropriate for particular groups of patients with special needs, such as women and children.

Research and development (R&D) on diseases prevalent in poor countries is lacking for several reasons. Donor governments and developing countries have not invested sufficient resources into research for these diseases. In 2007, the total contribution from Germany for neglected diseases was only 20.7 million Euros, or 0.12 per cent of its overall research budget.

Pharmaceutical companies do not prioritise R&D to address diseases of the developing world, due to lower financial returns in poor country markets. Furthermore, the WTO TRIPS Agreement, which in 1995 introduced twenty years of patent protection worldwide, failed to boost R&D in pharmaceuticals to satisfy the needs of developing countries, and it provides monopolies to pharmaceutical companies that result in unaffordable prices for medicines.

Only three new medicines for neglected diseases emerged out of global R&D activities between 1999 and 2004. This is woefully inadequate. Three main barriers hinder progress:

- **Insufficient financing:** R&D for neglected tropical diseases receives only \$1 out of every \$100,000 spent worldwide on biomedical research and product development, and only 16 percent of funding for product development partnerships (PDPs) is provided by governments of rich countries.
- **Lack of bold and creative thinking about incentive mechanisms:** New mechanisms, such as advanced market commitments, priority review vouchers, PDPs, and orphan drug programmes, should be commended for their support to vital R&D and are evidence of an openness to new ideas. However, each of these has its specific drawbacks, which need to be addressed before widespread implementation is planned.
- **Absence of coordination concerning R&D:** Without coordination within and between countries, resources are used less efficiently and important needs are neglected.

New ideas have recently emerged to improve R&D to address the diseases that most affect developing countries. Patent pools enable collective management of intellectual property (IP) for use by third parties for a licensing fee; facilitate follow-on innovation for appropriate formulations and fixed-dose combinations; while also reducing medicine prices through

generic competition. Prize funds expand the range of incentives for R&D beyond those that support the existing system of IP ownership, offering innovators a cash prize that reflects the contribution of a product to public health. Prizes are particularly effective for promoting access, since they do not require the cost of R&D to be recovered through high medicine prices.

In addition to incentives, building the scientific capacity of the developing world could potentially lower the costs of drug development; create new centres of innovation; broaden the range of health problems targeted by medical R&D; and ensure that R&D costs are shared more equitably between all countries. Development of local and regional manufacturing, regulatory functions, clinical-trial capacity, and scientific expertise would repay investment.

It is encouraging that these issues are receiving attention. Through the World Health Organization (WHO), an Inter-Governmental Working Group on Public Health, Innovation and IP (IGWG) was initiated to address the demands of developing countries for a global system of R&D that better reflects their needs. The IGWG produced a Global Strategy and Plan of Action in May 2008 that will serve as a roadmap to identify new means to deliver innovation, and ensure that existing technologies can be equitably shared in the interests of all.

From these collective efforts, a global framework for R&D should emerge. This has the potential to ensure that efforts to improve R&D are well coordinated, and will also empower developing countries to contribute to innovation. In this report, Oxfam argues that a Global Fund for Research and Development, linked to a global R&D framework, could play an immediate and positive role in improving R&D for the diseases that undermine public health in developing countries. Capital under such a Fund would be provided by governments worldwide, in proportion to their means, giving all countries a stake.

Ultimately, it is a combined responsibility of all countries to find ways to ensure global R&D is organised to improve human health; inability to pay should not disenfranchise a large majority of the world's population from access to effective healthcare. Oxfam recommends that:

1. The WHO, in collaboration with other multilateral agencies, should lead a concerted effort to establish a Global Fund for Research and Development of medicines. The Global Fund should be linked to a R&D framework. All countries should contribute to the Fund according to their GDP, and the philanthropic sector should also participate. All contributors should have a stake in setting priorities.
2. The R&D agenda of all countries, philanthropic foundations, the pharmaceutical industry, and product development partnerships should be set to include – in addition to discovery of new compounds and the development of new medicines – the adaptation of formulations suitable for developing country needs, and for population groups, including children and women.
3. New incentives for R&D, such as prize funds, which avoid patent pitfalls, or those that ensure IP is not a barrier to innovation, such as patent pools, should be implemented and evaluated by donors and developing countries with respect to their utility to meet particular needs. The TB prize fund and UNITAID patent pool serve as helpful

models for further development of these and other creative mechanisms.

4. Donor governments should scale up their contributions to R&D for diseases predominantly affecting developing countries through official development assistance and their own research budgets. Developing countries should prioritise R&D in their own budgets. All governments should coordinate their R&D efforts with universities, research institutions, and private foundations through the R&D framework. This framework could mirror other initiatives that will rationalise health aid for developing countries, such as the International Health Partnership (IHP).
5. Donors, including private philanthropic foundations, should follow internationally agreed criteria when prioritising their financial contributions for R&D. They should commit to: transparency of information concerning the amount and nature of their contributions to R&D; open access to the data that is produced; building the capacity of academics and research institutions in developing countries; assistance for technology transfer; long-term planning for sustainable clinical-trial capacity in developing countries; involvement of developing country governments and civil society in decision making; and making the resulting products affordable, including through open licensing of emerging products.
6. Pharmaceutical companies and universities should recognise the weaknesses of the IP system to respond to the need for new and adapted health products for the diseases of developing countries. They should support PDPs by providing expertise and access to compound libraries and continue to develop stand-alone or joint research centres tackling neglected diseases. They should cooperate in the early involvement of generic companies, biotechnology companies, and academia to devolve costs of parts of the R&D process, and to speed the delivery of effective new products.

1 Introduction

Scientific innovation can save millions of lives and reduce suffering and poverty. Yet insufficient resources are dedicated to develop new vaccines, diagnostics, and medicines to address the health needs of poor people. In 1990, a landmark study identified the '10/90 gap' – the fact that less than ten per cent of global health-research spending was dedicated to addressing diseases that predominantly afflict the poorest ninety per cent of the world's population.¹

Two reasons for the lack of R&D to address diseases prevalent in poor countries were the inability of the latter to purchase new products and the unwillingness of rich country governments to invest in research into these diseases. There were insufficient financial incentives for the pharmaceutical industry, which instead focused its efforts on developing medicines that would provide annual 'blockbuster' revenues of at least one billion dollars per medicine.

Nearly two decades later, the 10/90 gap remains.² R&D dedicated to combat neglected tropical diseases receives only US \$1 out of every US \$100,000 spent worldwide on biomedical research and product development.³ Between 1975 and 1999, only one per cent of a total of 1,393 new medicines was dedicated to the treatment of neglected diseases.⁴ Although R&D spending has increased in absolute terms, the situation has changed little. Thus, between 1999 and 2004, only three new medicines for neglected diseases emerged out of global R&D efforts.⁵

One critical moment in this debate was the adoption of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) by the World Trade Organisation (WTO) in 1994. This requires all countries, except least-developed countries (LDCs), to introduce a US-style intellectual-property (IP) regime, including a twenty-year term of patent protection for all fields of technology, including pharmaceuticals.⁶

The TRIPS Agreement, introduced by rich countries at the behest of the multinational pharmaceutical industry, works imperfectly as a means of encouraging innovation in rich

countries, but it has clearly failed to satisfy the needs of the developing world. In a 2006 report entitled 'Public Health, Innovation and Intellectual Property Rights', the World Health Organization (WHO) concluded that there was 'no evidence that implementation of the TRIPS Agreement in developing countries will significantly boost R&D in pharmaceuticals', since there were 'insufficient market incentives'.⁷ Moreover, by delaying competition from generic medicines in developing countries, IP protection results in unaffordable prices for medicines, with terrible consequences for millions of poor people.

The lack of medicines that address diseases of the developing world poses a serious threat to fulfilment of the human right to health and impedes achievement of the Millennium Development Goals.⁸ It may in the long term also affect developed countries, which are increasingly susceptible to neglected diseases.⁹ This paper identifies what governments and the pharmaceutical industry have accomplished so far to stimulate R&D for diseases that predominantly affect developing countries (labelled as Type II and Type III diseases by the WHO).¹⁰ While funding for R&D that addresses poor-country diseases has increased, it is still woefully insufficient and often supports uncoordinated efforts with potentially limited effectiveness.

Yet fixing funding problems will not be enough. A system that depends on ever-stricter imposition of IP rules, with resulting high prices and a lack of medicines to address diseases predominantly affecting developing countries, cannot be 'fixed' solely with aid money. Developing countries are ready to participate in a global system of innovation as equal partners, sharing the costs and benefits in new ways with the rich world. This report will explore new models which will harness R&D to improve human health more sustainably and affordably. Ultimately, all countries must find ways to ensure that global R&D improves human health, irrespective of the patient's ability to pay.

2 The Intellectual Property model fails to address the disease burden of developing countries

Over the past decade, Oxfam has campaigned with civil society worldwide to ensure that IP rules do not deny access to affordable medicines in developing countries.

The Doha Declaration on TRIPS and Public Health, agreed by all WTO Member States in November 2001, affirmed that public health should always take precedence over the enforcement of IP rights. Yet since 2001, rich countries and pharmaceutical companies have ignored the Doha Declaration and pursued an aggressive agenda to subject the developing world to even stricter IP protection, through free-trade agreements and unilateral pressure.¹¹

An R&D system exclusively based on IP does not generate sufficient economic incentives for pharmaceutical companies to develop medicines needed predominantly in poor countries. In fact, many pharmaceutical companies have downsized or shut down their infectious-disease R&D divisions.¹² Furthermore, IP often acts as a barrier to innovation itself. 'Patent thickets'¹³ severely limit the ability of researchers to develop new treatments and technologies.¹⁴ Increasingly, the existing approach to R&D is failing rich countries too, with few pharmaceutical companies successfully replenishing their drug pipelines.¹⁵

Statistics indicate that a dearth of R&D means that many medicines, diagnostics, and vaccines needed to prevent and treat infectious diseases are inappropriate or simply do not exist.¹⁶ The consequences for poor people are dramatic. Infectious diseases remain the main cause of death in Africa, claiming the lives of millions of people every year, especially those of women and children.¹⁷ Neglected tropical diseases¹⁸ kill 500,000 people every year, and also cause chronic disability and social stigma for millions.¹⁹ The drug pipeline for treatments that would ensure safer pregnancy and childbirth is severely constrained: only 17 medicines underwent evaluation between the preclinical and preregistration phases from 1980 to 2007. By comparison, 660 new medicines have been evaluated

for cardiovascular disease over the same period.²⁰ Diseases which have been mostly controlled in the rich world, such as tuberculosis, are contributing to an on-going health crisis across the developing world. See Box 1.

Box 1: The critical lack of TB diagnostics, vaccines, and medicines

Nearly two million people die annually from tuberculosis (TB). Every year, half a million patients develop multi-drug-resistant TB (MDR-TB), causing more than 130,000 deaths.²¹ A 2006 survey found resistance to TB medicines in all 79 countries surveyed, with China, India, and Russia accounting for more than half of all MDR-TB cases.²² Furthermore, one-third of all HIV-positive individuals are co-infected with TB.²³

Yet the current TB vaccine, which is only partially effective in infants, and does not confer immunity to adults, was introduced in 1923, and the most recent first-line TB drug regimen was developed in the 1960s.²⁴

IP-dependent systems of R&D mean that many medicines are inappropriate for particular groups of patients, especially women and children, because there are fewer economic incentives for patent holders to prioritise the development of such medicines. Thus, although more than half of all HIV-positive people in sub-Saharan Africa are women, few studies have addressed the effects of antiretroviral medicines on pregnant or lactating women.²⁵

Children's needs for safe and practical products have been severely neglected, in part because they form an unprofitable sub-set of the market. Since their physiological systems are immature, children require treatment with age/weight-related dosages of medicines, and formulations must be palatable and practical to administer. But children have not been included in clinical trials, and safe age-appropriate dosage forms have not been established. Some experts estimate that well over 60 per cent of medicines used to treat children have not been licensed or authorised for use in this population.²⁶

Concerns about the lack of R&D have spurred developing countries to action, especially at the WHO. From 2006 to 2008, an Inter-Governmental Working Group on Public Health, Innovation and Intellectual Property Rights (IGWG) addressed the demands of developing countries for a global system of R&D that better reflects their needs.²⁷ The negotiations produced a Global Strategy and a nearly complete Plan of Action.²⁸ The strategy recognises IP as a key feature, but it calls

upon the WHO, and all countries, to identify new means to deliver innovation, while also ensuring that existing technologies can be equitably shared in the interests of all.

Countries and pharmaceutical companies must heed the findings of the IGWG and implement new approaches to R&D that improve on and go beyond the IP-based model, while also increasing the capacity of developing countries to engage in R&D. While both governments and the pharmaceutical industry have introduced a few reforms, much more must be done to increase R&D funding, improve implementation, and facilitate greater sharing of knowledge, all without sacrificing access to resulting medicines or vaccines in developing countries.

3 Greater public financing for R&D is urgently needed

More public financing for drug development for the diseases of poor countries is needed, and this should be an obligation of rich and poor countries.

Public financing for R&D requires inputs both to 'push' and to 'pull' financing. 'Push financing' means paying for basic scientific research that is translated into new and adapted medicines, or directly paying costs associated with bringing a medicine to market. 'Pull financing' involves creating financial or market incentives for the private sector, or a public-private entity.

Most innovative medicines emerging from the pharmaceutical industry have their origins in publicly funded research. A US Congress report in 2000 found that of 21 innovative medicines introduced between 1965 and 1992, 15 were developed by applying knowledge or techniques derived from government-funded research.²⁹

Despite the urgent needs, donors are failing abjectly. Few rich countries can identify their funding inputs for the R&D priorities of developing countries, and so cannot judge their performance. Families USA, a health advocacy group,

examined the R&D budget of the US government in this respect and noted that – in order to be effective – the additional push financing for R&D for diseases prevalent in developing countries would require an increase in the budget of the National Institutes of Health (NIH) of 6.7 per cent in 2009, in addition to financing for other government institutions. Although US funding levels are insufficient, funding for neglected diseases from the European Union (EU) and Japan is even worse. Médecins Sans Frontières (MSF) noted that the total contribution from Germany, the world's third largest economy, for neglected diseases was only 20.7 million Euros in 2007, or the equivalent of 0.12 per cent of the German research budget.

Existing R&D mechanisms supported by rich countries are also severely under-funded. Over the past decade, numerous product-development partnerships (PDPs) have been launched to develop new medicines and vaccines, through a combination of resources from the public sector, philanthropy, and the pharmaceutical industry. While PDPs have certain problems that limit their effectiveness, these entities should be supported as one approach to generate R&D for neglected diseases. Yet only 16 per cent of funding for PDPs is provided by rich countries, in comparison with philanthropic foundations. The Gates Foundation provides 79 per cent of overall financing. Some countries, such as Germany, have given no money whatsoever, while the European Commission, as the primary funding source on behalf of the entire EU, has provided little support.³⁰

This neglect of PDPs is occurring at a particularly inopportune time. PDPs have assembled a pipeline of 64 candidate compounds that must undergo clinical trials to determine their effectiveness. Significant donor funding will be required to complete these clinical trials.³¹ The lack of funding towards R&D for neglected diseases is happening just as rich countries are currently increasing spending on their own pharmaceutical companies to produce medicines intended primarily for the rich world. Some rich-country governments are investing more money in R&D, especially through push financing. This includes investing in basic scientific research,³² and supporting

links between pharmaceutical companies and academic institutions to develop new medicines.³³

4 IP-based R&D mechanisms have limited effect

In recent years, new models of R&D have emerged to harness donor funds for pro-poor innovation, especially: Advanced Market Commitments, Priority Review Vouchers, Product-development Partnerships, and Tax Credits. Oxfam supports all four approaches, but believes that problems with each model limit their effectiveness.

The advantages and disadvantages of each model are discussed below. Common problems with these new R&D models include the following:

- Funds not focused sufficiently on true innovation.
- Emerging products may be unaffordable, particularly in middle-income countries with large numbers of poor people.
- Emerging products may be inappropriate in poor countries.
- Knowledge cannot be shared, on account of the granting of IP rights which limit follow-on innovation and broader scientific research.
- Inadequate governance and limited transparency negatively affect their design and implementation.

Advanced Market Commitments (AMCs)

An AMC is an incentive to stimulate the commercial development and rapid introduction of new health products (particularly vaccines) that are not available in poor countries because of the lack of market demand. Donor countries enter into a legally binding guarantee that if a vaccine is developed against a particular disease, they will pay a fixed price for that

vaccine's uptake in developing countries. The guarantee is linked to technical standards that must be met by the vaccine. According to their designers, AMCs are structured to allow several firms to compete and develop the best possible vaccines.

Yet the first AMC, launched by the G8 in 2005, was applied at a cost that is too high for donors and developing countries. See Box 2.

Box 2: The pneumococcal AMC: a cautionary tale for donors

The first AMC allocated US \$1.5 billion to the purchase of a vaccine to prevent pneumococcal disease, which is responsible for the deaths of 1.6 million children every year. Donors included Canada, the United Kingdom, Russia, Italy, Norway, and the Gates Foundation.³⁴

This AMC is not an appropriate use of donor funds. Although there is a huge burden of pneumococcal disease among poor children, a large market for the vaccine exists also in developed countries.

When the AMC was launched in 2005, two candidate vaccines were already well under development by major pharmaceutical companies and moving towards regulatory approval. Therefore, it cannot be claimed that this AMC provided an incentive for a vaccine that otherwise would not be developed. Instead, it is a procurement contract to encourage companies to meet demand in poor countries at subsidised prices.

This AMC comes at a high cost for donors and developing countries. Donors pay high, up-front prices of at least US \$7 per dose, in part because of the successful bargaining by pharmaceutical companies.

It is unclear whether the price of the vaccine will be affordable in poor countries after the AMC fund is exhausted. The maximum, long-term 'tail-price' of the vaccine is US \$3.50/dose, a figure which equates to per capita expenditures on health in many LDCs. Neither the Global Alliance for Vaccines and Immunizations (GAVI) nor donor countries considered contracts that could introduce production of the vaccine in emerging markets, which could have fostered competition and rapidly lowered prices.

Since price negotiations and costs are non-transparent, it is unclear how much additional profit pharmaceutical firms will obtain from the AMC. Estimates by MSF indicate that profits could exceed US \$600 million, bearing in mind the vaccine's application in rich countries.³⁵

It is essential to consider measures that encourage a 'healthy market' that stimulates development of new vaccines and ensures long-term affordability. Earlier phased integration of competition from generic-vaccine manufacturers would avoid the risk of creating a monopoly, and the risk of countries bearing an unfeasible financial cost at the end of the agreement.

Despite these concerns, donor countries and supporters of the AMC model are already planning to launch subsequent AMCs, particularly for a vaccine against TB or malaria.³⁶ In such cases, the lessons from the first AMC suggest clear guidelines to follow. Specifically:

- An AMC should be applied to vaccines which will not be developed unless there is a large financial incentive to pull the vaccine through drug-development and clinical trials.
- Donors' funding for an AMC should not be counted as a part of annual R&D spending until the monies are actually spent. This could be multiple years after a donor commitment because of the time gap between commitment to spend and the final development of the vaccine.
- AMC monies for innovation should not be used as a procurement fund to purchase nearly finished vaccines.
- An AMC should ensure low prices for developing countries, especially through competition among low-cost manufacturers. The upfront price paid by donors should be as low as possible, in order to use the monies efficiently. The tail price after the AMC ends should be affordable by developing countries.
- Financial rewards to pharmaceutical companies should be far less if the vaccine has application in rich-country markets.
- The AMC should encourage follow-on innovation. Allocated funds should be given in stages, so that initial rewards for a first vaccine do not preclude new manufacturers entering the market and capturing AMC funds.
- Donors' commitment to an AMC should be additional to other R&D initiatives such as academic research.

Access to the vaccine should be guaranteed to all developing countries. The first AMC-subsidised vaccines are available to only 62 poor countries that are members of GAVI, which administers the AMC.³⁷ Thus, countries not included on this list, especially middle-income countries (MICs), will have to pay higher 'tiered' prices to provide sufficient returns to

pharmaceutical companies. The system carries the risk that MICs may not be able to pay higher prices, thus depriving poor people in MICs of access to the vaccine.

Oxfam has supported the use of tiered pricing in principle. However, it is unacceptable to create trade-offs between different groups of poor people, whose fates are sealed by whether or not their country benefits from GAVI's negotiated price.

To ensure affordability in MICs, GAVI, in consultation with donor and recipient countries, may consider measures such as expanding its coverage to MICs, with lower prices and subsidies from GAVI; or requiring donors and MICs to offer an up-front payout for IP rights in all developing countries. The vaccine could then be produced by emerging-market manufacturers who compete to offer the vaccine at lower prices in developing countries.

Product-Development Partnerships

PDPs are non-profit entities with public, private, and pharmaceutical-industry resources dedicated to R&D on one or more Type II or III disease. PDPs have been lauded as the ideal solution to the lack of medicines for diseases that disproportionately affect developing countries. They have proved effective in promoting and initiating considerable R&D activity. Yet their utility as mechanisms for supplying new medicines for neglected diseases remains to be shown: only three new products have emerged from their drug pipelines, although there are promising candidates.³⁸

PDPs have advantages, including the following:

- They are able to complete the entire cycle of R&D at far lower cost than the pharmaceutical industry working on its own, and they can do so in a more transparent manner. PDPs have publicly estimated the average cost of drug development at US \$115–240 million, if undertaken by PDPs, compared with the industry's estimates of US \$800 million.³⁹

- As non-profit entities, PDPs can take access into account.⁴⁰ Non-patented products will encourage generic competition and price reductions.

However, there are many problems facing PDPs which limit their potential. Firstly, PDPs co-ordinate their activities only to a limited extent, and must compete for donor funds to complete drug development – a reality that makes mutual learning and comparisons of methods difficult. Lack of coordination also results in an inefficient use of resources, such as repeated demand forecasting. PDPs seldom share lessons learned from their experiences, including appropriate business strategies to manage IP.

Furthermore, PDPs are struggling to define their relationship with the pharmaceutical industry, upon which they heavily depend for access to scientific data, compound libraries, and infrastructure to conduct R&D. Some PDPs are unable to acquire IP from an industry partner and must accept monopoly pricing for products.⁴¹ Companies are less likely to make concessions on IP when potentially profitable markets are at stake, as is the case with diseases such as HIV and AIDS and dengue fever. If pharmaceutical companies retain control of IP for MICs, prices in those countries may not be affordable.

Donors could improve access by providing additional financial and fiscal incentives (such as purchasing IP rights for developing countries), or by mandating that any IP emerging from a donor investment is managed by the PDP. When PDPs are unable to secure control of IP, tiered pricing in developing countries must include differential pricing within MICs.⁴²

It is not clear if PDPs that hold rights to IP will share these rights to encourage generic competition, or instead will rely on tiered pricing with high prices for well-off developing countries. The malaria drug ASAQ, developed by the Drugs for Neglected Diseases Initiative (DNDi), is patent-free, which will allow different companies to compete on price. Although economies of scale may allow lower prices from a single producer, experience has shown that lowest prices are delivered through competition.

Both PDPs and governments must also ensure greater access to and sharing of knowledge. Since the WHO Global Strategy calls

for the promotion of public access to the results of government-funded research, PDPs should share knowledge with each other and among their academic and industry partners.⁴³ PDPs should also influence pharmaceutical companies and universities to provide access to compounds and related knowledge.⁴⁴ Private firms may 'free-ride' on publicly funded R&D that PDPs openly share, without sharing their own findings in return. One commentator described the one-way movement of knowledge and research findings to the private sector as accompanied by a 'giant sucking sound'.⁴⁵ While publicly funded knowledge in this case can encourage innovation in the private sector, the industry's failure to share information could hamper the development of additional medical technologies and knowledge.

Priority Review Vouchers (PRVs)

The PRV is a new incentive mechanism recently incorporated into US law.⁴⁶ In exchange for successfully launching a new medicine to treat a neglected disease, a pharmaceutical company or other entity (a PDP, for example) receives a voucher from the US Food and Drug Administration (FDA) for fast-tracked review of any other medicine.⁴⁷ This voucher is fully transferable to a third party. By applying the voucher to a medicine that will have extensive sales in the developed world, the company extends the time for marketing the medicine at monopoly prices by up to 18 months. Experts estimate that the voucher is worth up to US \$321 million.⁴⁸

The PRV could be an important source of funding to stimulate R&D within pharmaceutical or biotechnology companies, or to ensure that PDPs can complete a neglected-disease project.⁴⁹ However, the PRV raises some concerns, including the following:

1. Affordability of neglected-disease medicines in middle-income countries

Under US legislation, the company maintains control of IP for the neglected-disease medicine at stake. Even if tiered pricing is applied to its sales, MICs may have to pay too high a price. Small biotechnology companies, which often have limited

products in their portfolio, are particularly sensitive to their commercial returns and will seek higher prices in MICs in order to recoup their investments and secure adequate profits.⁵⁰ Appropriate pricing strategies for MICs should be instituted, or preferably, IP rights in developing countries should be surrendered in exchange for a voucher.

2. Appropriateness of neglected-disease medicines

There are no incentives or obligations for pharmaceutical companies to develop medicines that meet the conditions of use in poor countries, or the particular needs of sub-groups such as women or children. Since successful companies retain IP rights, other manufacturers are barred from producing better formulations that would improve usability in poor countries, including fixed-dose combinations.

There are ways to rectify this problem, including: (1) as a precondition for FDA approval, the relevant formulation of a medicine is approved for use by a panel of US and developing-country experts,⁵¹ or (2) legislation requires IP to be shared with follow-on innovators.⁵²

3. Misallocation of donor resources under the PRV

In some circumstances, it appears that the PRV provides an excessive reward for R&D. Since the PRV is rewarded for a medicine when it is first registered in the USA, companies that have already received adequate incentives and have registered a medicine elsewhere will receive a windfall profit in the USA for no better reason than that it had not been previously registered there.

Novartis, which developed the anti-malarial medicine Coartem, will receive a PRV, and a potential profit of US \$321 million, solely for registering Coartem with the US FDA, even though the medicine is already in widespread use.⁵³ Allowing unearned windfalls in this way undermines the credibility of the PRV as a valid mechanism to stimulate R&D for neglected diseases; the legislation should be amended.

Orphan Drug schemes and tax credits

Orphan Drug schemes in the USA and EU offer additional market exclusivity and financial benefits for new medicines treating diseases that affect relatively few people in the country that awards the benefit.⁵⁴ These schemes can also be applied to medicines for diseases that predominantly affect developing countries. The credits reward a manufacturer with tax benefits and an extended patent term. However, extended market exclusivity under an Orphan Drug scheme may induce manufacturers to charge unaffordable prices in the search for profitable returns.

Tax credits are often provided as part of a package of benefits within the Orphan Drug scheme, and also as a stand-alone benefit. In the USA, a tax credit is provided for 50 per cent of the cost of clinical trials that are conducted for R&D for rare diseases. Some countries have introduced additional tax credits to boost research on specific diseases that are viewed as 'priority' diseases for developing countries. The UK has an existing programme which provides a tax credit for R&D for HIV and AIDS, TB, and malaria.

These schemes provide important private incentives to encourage new R&D. Yet it is unlikely that they function effectively on their own to create incentives for R&D for diseases prevalent in developing countries. The WHO noted that Orphan Drug Credits are insufficient to stimulate innovation for neglected diseases, because extended market exclusivity in a developed country does not take into account the absence of a market there. Tax credits function effectively as an incentive only where there are anticipated profits.⁵⁵

Thus, to ensure that tax credits function effectively, countries could consider designing credits that work in concert with other incentive schemes, such as a PRV, or credits that target contributions made by pharmaceutical companies to PDPs. These could work across countries to build incentives to encourage private-sector research.

5 R&D financing must be participatory, transparent, and co-ordinated

Governance and transparency

High standards of governance and transparency are essential for the proper functioning of various R&D mechanisms. Yet institutions that either design R&D incentives or conduct R&D for diseases prevalent in developing countries themselves do not provide sufficient representation of developing-country interests. Furthermore, decision making is often non-transparent. For example, it appears that all major decisions about the recent pneumococcal AMC were made by the donor committee. A recent journal article noted: 'Not one "global" [PDP] is led by a person who is a developing-country national and not one resides within one of the developing countries severely affected by neglected infectious diseases.'⁵⁶

PDPs vary greatly in terms of including representatives from developing countries and civil society. Yet engaging them from the inception of a PDP is crucial if countries are to adopt its products into their health systems. Those PDPs that involve national laboratories and consult with developing-country governments are more likely to incorporate their perspectives. For example, DNDi works with public laboratories in Brazil, Kenya, and India.

There should be significant and meaningful representation of developing countries on all R&D decision-making bodies. Participation by developing countries can ensure that new products are appropriate and affordable, and that they fit with national health plans and priorities. But calls for increased involvement of developing countries in R&D governance will carry much greater weight if such involvement is perceived as a right, rather than a privilege. Developing countries should thus contribute financially to the promotion of R&D according to their capability.

There is also a lack of transparency with respect to the cost of R&D and production under some new mechanisms; this information is necessary to enable donors and patients to assess costs. For example, although GAVI has instituted a

comprehensive evaluation programme for its first AMC, it did not evaluate the actual costs to pharmaceutical companies of producing the pneumococcal vaccine, and it could not relate the deal to the costs of producing the same vaccine in other countries. This creates concern among civil-society groups that donors are paying an unnecessarily high price for a vaccine, thereby reaching fewer poor children across the developing world.

Co-ordination

R&D for neglected diseases is rife with examples of poor co-ordination within and between countries. Firstly, countries do not internally co-ordinate R&D expenditures on poor-country diseases. A lack of co-ordination among different ministries means that governments are unable to identify overall R&D financing accurately. Thus, it is difficult to set targets either to meet global needs for R&D for treatments for neglected diseases or to hold governments accountable for mandated targets.

Countries do not co-ordinate R&D expenditures with one another, except when they jointly fund the same programme (for example, the pneumococcal AMC).⁵⁷ This lack of co-ordination leads to a highly inefficient use of resources and often creates major gaps in R&D spending. Scarce funding is often spread among a variety of initiatives and across multiple agencies that finance R&D for poor-country diseases.⁵⁸ By contrast, the pneumococcal AMC, which was funded jointly by five countries and the Gates Foundation, with GAVI serving as a secretariat, demonstrates that deliberate co-ordination and collaboration can ensure sufficient funding for a targeted outcome.

A lack of co-ordination within and between countries also negatively affects priority setting with respect to different diseases. Within governments, it can mean that diseases that do not have an effective champion often do not get the funding that they need, while those diseases that have captured donor and media attention receive most of the available funding, even if it is insufficient.

Funding priorities for new and better medicines, diagnostics, vaccines, and formulations must not be based upon the degree

to which there is a public outcry. For example, new antibiotics to address growing drug resistance have not been a priority for the public or private sectors. There is still hardly any research on diseases such as Ebola haemorrhagic fever or Marburg virus.⁵⁹ Inadequate priority setting is also reflected in donor spending. The European Commission spent 420 million Euros on R&D for HIV and AIDS, TB, and malaria during its Sixth Research Framework Programme, while all other neglected diseases combined received only about one-tenth of that funding.⁶⁰ A November 2008 meeting on 'poverty-related diseases' hosted by the European Commission will focus primarily on TB, HIV and AIDS, and malaria, whereas other diseases are only added as an afterthought.

Entities that conduct research, especially PDPs, cannot ensure adequate priority setting. PDPs compete with one another for resources from donors. In this 'free-for-all', diseases which are not hosted by a PDP, or are hosted by a smaller PDP, could get fewer resources, despite a pressing disease burden.⁶¹

There are new initiatives to track funding, particularly a new project hosted by the George Institute for International Health in Australia. However, it will not make a difference unless rich countries use its findings to consciously co-ordinate their efforts internally and with one another, and with important private sources of financing such as trusts and foundations.

A more formalised framework is needed in order to co-ordinate the funding initiatives of rich countries and developing countries (see below). This could mirror other initiatives that will rationalise health aid for developing countries, such as the International Health Partnership (IHP), or that are functioning as an information facilitator, such as the Convention on Biological Diversity's Clearing House Mechanism.⁶² As with the IHP, this would also provide an avenue for recipient countries to participate and provide input about actual funding needs, priorities, and approaches that are appropriate in their countries. Such a framework could also improve transparency regarding the contributions of pharmaceutical companies, and act as an incentive through recognising their inputs.

Finally, countries working together under an institutional framework should examine whether bundling together

different incentive mechanisms could improve the likelihood that a pharmaceutical company or PDP will develop a new medicine. This could also ensure that donors do not provide excessive rewards to a pharmaceutical company or a PDP that had already received a reward or incentive from a different country or financing entity.⁶³

6 Moving beyond the IP system

The exclusive reliance on patent monopolies as the only mechanism for innovation remains a major barrier to R&D for diseases that predominantly affect developing countries. Yet there are new approaches under discussion which improve knowledge sharing and follow-on innovation, or which avoid reliance on patent-based monopolies as an incentive mechanism for private firms.

Patent pools

One mechanism under consideration at UNITAID (the international drug-purchasing facility) and under the WHO Global Strategy is the use of patent pools. A patent pool is an agreement between two or more parties to license one or more of their patents to a collective 'pool' which can be used by any third party. This agreement usually formulates standard licensing terms and determines the level of royalties that each patent owner will receive from third parties for use of licensed patents.⁶⁴ The mechanism acknowledges that innovation builds on the knowledge and findings of previous researchers. A patent pool overcomes the thicket of patents that prevents researchers from sharing and using knowledge to develop new leads for vaccines or medicines, and it can also improve access to existing medicines.⁶⁵ Thanks to the diligent efforts of civil-society groups and countries that contribute to UNITAID, a first patent pool that can spur greater innovation and access to medicines may not be far from becoming a reality. See Box 3.

Box 3: UNITAID patent pool

UNITAID recently approved, in principle, establishing a patent pool for medicines. The collective management of licences would facilitate licensing to generic firms and thus bring prices down. Costs for second-line antiretroviral treatments would most likely decrease. Furthermore, management of IP from multiple companies will assist follow-on innovation, allowing the utility of existing medicines to be enhanced through fixed-dose combinations and paediatric formulations.

Some difficult questions remain at UNITAID, including whether the patent pool can be applied to medicines for other diseases, and whether generic medicines produced under the licence agreements can be sold to MICs. In 2008, at least three multinational pharmaceutical companies have tentatively offered their support for the patent pool.⁶⁶

Prize funds

Member States of the WHO, under World Health Assembly Resolution 60.30, called for new incentive mechanisms that address the de-linking of the costs of R&D from the price of medicines. The fundamental challenge is that the existing incentive model relies on high medicine prices to recuperate the cost of innovation, thus denying affordable access to medicines in developing countries.

Prizes constitute an innovative 'pull' mechanism, which may overcome the linkage of innovation and drug prices. Innovators are offered a cash prize, which reflects the product's contribution to public health. While prizes enable an innovator to maintain a patent, it requires the recipient of a prize to surrender monopoly rights in exchange for the reward, thereby ensuring generic competition and drastic price reductions. The instrument can also stimulate follow-on innovation, since prize winners are asked to place scientific knowledge in the public domain.

Prizes have increasingly been lauded and used by various actors, including the pharmaceutical industry. For example, the pharmaceutical company Eli Lilly established its own prize programme to stimulate innovation for new medical research tools.⁶⁷ There have also been attempts to introduce prizes as a government-funded incentive. A 2007 bill introduced in the US Senate – the Medical Innovation Prize Fund Act⁶⁸ – would,

upon marketing approval of a new medicine, offer a drug developer a share of a fund that would be split among eligible innovators roughly in proportion to the health impact of their products.⁶⁹

Developing countries, in co-operation with prize-fund and open access advocate Knowledge Ecology International, have also proposed establishing a prize fund as a viable alternative to existing incentives for drug development. For example, Bolivia and Barbados submitted several prize fund proposals to the WHO to stimulate innovation, including a prize for a simple, low-cost TB test (see Box 4).⁷⁰

Box 4: Tuberculosis Diagnostic Prize Fund⁷¹

The currently available TB diagnostic test was developed more than 100 years ago. It requires the microscopic examination of sputum over several days by a qualified health worker. It is not suitable for quick diagnosis in poor settings staffed by community health workers.⁷²

The Tuberculosis Diagnostic Prize Fund would encourage innovation through three streams of funding:

1. A prize worth US \$100 million for introducing a diagnostic test that can be manufactured for less than \$1 per unit, can easily be distributed and applied in developing countries' health systems, shows the result within three hours, and returns a high percentage of correct results. The winner would have to grant licences to all patents, data, and expertise needed to produce the diagnostic test competitively worldwide.⁷³
2. Smaller technical-challenge prizes to be awarded for reaching specified benchmarks en route to the specified result.
3. Biannual 'best contribution' prizes for the most significant publicly available contribution to expertise needed to reach the result.⁷⁴

Another prize proposal, developed by Incentives for Global Health (IGH), differs from others in that it actually enables an innovator to maintain a patent and a monopoly.⁷⁵ The Health Impact Fund (HIF) is intended as a large international prize fund that creates incentives for the development of any new medicine or vaccine that has a demonstrable health impact. Fund recipients would receive a share of a specified annual disbursement over a ten-year period that is proportional to the product's health impact.⁷⁶ To ensure access, the fund would require the successful company to sell the product worldwide at an 'administered price near the average cost of production

and distribution' during the disbursement period.⁷⁷ Registrants must also permit the fund administrator to issue licences to generic competitors; although only for those countries where the patent holder cannot guarantee adequate supply, and after the reward period has ended. However, the HIF promotes neither widespread generic competition nor follow-on innovation for appropriate formulations and combinations because the medicine would continue to be under monopoly.⁷⁸

The implementation of prizes poses significant challenges. Prizes that base payment on relative medical benefits or on best contributions must find reliable means of measuring the relative medical benefits of various products and the relative contributions of researchers in an accurate and unbiased way.⁷⁹ Donors must determine how prizes can be awarded for the final product as well as for intermediates. The latter prizes would be attractive to innovators, particularly in academia, smaller companies, and companies in developing countries.

7 Encouraging capacity to conduct R&D in developing countries

Rich and poor countries must make investments in strengthening the scientific capacity of the developing world. Potential benefits would include lower drug-development costs, new centres of innovation, greater capacity to address a range of diseases, and a shared stake in appropriate products for public health.

To deliver these benefits, developed and developing countries should invest in the development of local and/or regional manufacturing and regulatory capacity, better use of existing clinical-trial capacity, and scientific expertise. Donor countries should abide by aid-effectiveness principles introduced in 2005 and renewed at the 2008 Accra summit on aid effectiveness.⁸⁰

Local production

Developed countries could reduce prices over the long term by investing in developing local manufacturing capacity. LDCs are

exempt from implementing TRIPS until at least 2016, and can therefore legitimately manufacture new medicines still under patent. In the long-run, viable local production sites could stimulate local scientific capacity in universities for the adaptation of products to local health needs, especially new combinations and formulations.⁸¹ However, local pharmaceutical production faces a number of technical challenges, such as scientific capacity, quality-assurance regulation, and the availability of human and technical resources. Market issues also need to be addressed, including ensuring viable economies of scale that can make the venture profitable for producers and create sufficient production to reduce prices adequately.

South–South co-operation in this area offers new possibilities and should be encouraged. Under a joint-venture agreement, one Ugandan pharmaceutical company has matured in recent years from re-packaging medicines to assembling formulations and now supplies 10 per cent of the domestic market.⁸² The agreement involves a prominent Indian generic producer which provides technological support, intermediates, and expertise in a package of technology transfer. Co-operation among developing countries could strengthen the pharmaceutical sector considerably, for example by harmonising quality assurance and creating regional markets for locally produced medicines, thereby promoting economies of scale and eliminating non-tariff trade barriers.⁸³

Clinical trials

Clinical trials usually constitute the largest single cost – up to 60 per cent⁸⁴ – of drug development, and thus are frequently seen as the bottleneck in drug development. Increasingly, clinical trials have been outsourced to developing countries. It is estimated that clinical trials conducted in India are up to 60 per cent less expensive than in the USA.⁸⁵ Trial participants can be recruited faster, reducing the trial period by at least six months. This increases the period during which a firm can sell a medicine under patent.⁸⁶ Hosting clinical trials is lucrative for local firms; in India it is a fast-growing industry.⁸⁷ More importantly, the availability of a large pool of ‘treatment-naïve’ patients, facilitating tests for efficacy of a medicine and against

the 'real-life needs of patients',⁸⁸ is a critical factor in developing medicines against all diseases.

The majority of developing countries face a number of challenges in the conduct of clinical trials.⁸⁹ Capacity and training of scientific staff and health workers to collect data and attend to trial participants are lacking, and demands on staff may divert scarce human resources away from other duties in weak health systems.⁹⁰

Many countries have only rudimentary technological infrastructure. Laboratory facilities, appropriate clinical settings, and even continuous electricity supplies are lacking. For many diseases it is difficult to reach trial participants in remote rural areas and ensure their compliance with trial procedures and follow-up, and there is a lack of simple diagnostic tools to confirm that patients are suffering from a particular disease.⁹¹

In many developing countries, regulatory capacity regarding the quality of medicines and ethical standards of clinical trials is also very weak, and informed consent is not always properly obtained. Another ethical concern is the fate of clinical-trial participants from poor countries upon completion of clinical trials.⁹²

Large funding agencies and bilateral donors are reluctant to build capacity in a sustainable manner.⁹³ Awareness is slowly changing, as some donor countries, including the USA and EU, are making greater contributions to improving the clinical-trial capacity of developing countries.⁹⁴ See Box 5.

Box 5: The European and Developing Countries Clinical Trials Partnership (EDCTP)⁹⁵

The EDCTP is a partnership between 14 EU Member States, Norway, Switzerland, and sub-Saharan African countries. It focuses on accelerating the development of new and improved medicines, vaccines, and microbicides against HIV/AIDS, malaria, and TB, especially in the latter phases of clinical trials in sub-Saharan Africa, and it supports multicentre projects to build capacity for clinical trials. In June 2008, the Partnership announced that more than €80 million (around US \$124 million) will be injected into African medical research.⁹⁶

Until now, funding has mainly been provided by large donors, such as the EDCTP and a joint TDR and Gates Foundation

initiative. There should be increased funding by other bilateral donors, including academic exchanges and specialty training.

Developing indigenous scientific expertise

Long-term funding for scientific co-operation and training can enhance the capacity of developing countries to achieve their own innovation goals, for example by adapting existing medicines to local conditions. Significant financial assistance is needed so that the diseases of the developing world can be tackled through indigenous research efforts.

A few partnerships have already been established, such as a series of programmes hosted by TDR, or by the John E. Fogarty International Centre for Advanced Study in the Health Sciences in the USA (see Box 6). Other US research efforts hosted in developing countries have often relied on military resources.⁹⁷

Box 6: John E. Fogarty International Centre for Advanced Study in the Health Sciences⁹⁸

The Fogarty Centre provides research grants for collaborative research and capacity-building projects relevant to low- and middle- income nations. Furthermore, institutional training grants are intended to enhance research capacity in the developing world. In sub-Saharan Africa, the Centre supports activities in about 20 countries, where 30 per cent of the funds support research into HIV and other sexually transmitted diseases, and 12 per cent is invested in research into non-communicable diseases.

Other governments have shown interest in such efforts, but have not yet matched their commitments with adequate funding. For example, as part of the EU–Africa Strategic Partnership and the EU–Africa Action Plan (2008–2010), EU Member States passed a resolution which emphasises ‘...*the need to increase the involvement of African scientists in international collaborative science and research and development (R&D) projects in order to keep and develop R&D knowledge in Africa ...*’⁹⁹ However, this useful recommendation has to be translated into substantive and long-term funding to encourage scientific co-operation. Developing countries also need to invest domestic resources in enhancing scientific and clinical trial capacity.

8 Building a global framework for research and development

Public-health needs, especially in the developing world, continue to rely on inadequate and insufficient *ad hoc* initiatives. A systematic global approach to R&D is required.

Over the next seven years the WHO, through the Global Strategy and Plan of Action, should continue to lead the way for all countries to work collectively to develop new sources of financing and innovation, to share the costs of R&D, and to ensure that any system of R&D meets the needs of all countries and all people.

Is a global approach to R&D possible?

The award of global monopolies to sell medicines implies a duty to ensure that medicines are created and traded to meet the needs of all people. This duty has not been met. But developing a new global approach to R&D will be difficult, especially given entrenched attitudes that regard linking the cost of R&D to high prices for medicines via the IP system as the sole incentive for innovation. However, trends in the pharmaceutical industry and improved research capacity in countries such as India, China, and Brazil have made a shared approach to R&D possible. The industry itself is adapting to new realities and opportunities, and is increasingly recognising that a lack of innovation for developing countries threatens the industry's social licence to operate.

Companies are relying on emerging markets as future centres of growth.¹⁰⁰ GlaxoSmithKline has established emerging-market divisions in recognition of their sales and potential for future growth, and cost-saving opportunities. In 2008, while industry growth in the richest countries ranged from 1 to 6 per cent, growth in the largest economies in Latin America (Brazil, Argentina, and Mexico) ranged between 5 and 20 per cent.¹⁰¹ Although these markets are small, the trend of growth is obvious. Moreover, companies are identifying diseases once viewed as relevant only to poor people as potential targets. Some neglected diseases such as TB are increasingly appearing in developed countries.¹⁰²

Companies have also increasingly enlisted the resources of developing countries to engage in drug development and clinical trials, and to manufacture medicines and vaccines at lower prices. While most relationships involve outsourcing some aspect of drug development, some multinational companies are sharing IP (via licensing agreements) as a reward for sharing the costs of innovation.¹⁰³ The strategies of emerging-market firms for the management of IP and promotion of access should be monitored.

Some developing countries are also making strides with their own medical innovation and production. Recently Brazil announced that public research institutions have discovered three potential antiretroviral molecules from natural sources that promise effectiveness and less toxicity.¹⁰⁴ Cuba developed the first vaccine against Meningitis B,¹⁰⁵ and India is one of the world's largest producer of the diphtheria-pertussis-tetanus vaccine.¹⁰⁶

Brazil has also entered into a partnership with the biotechnology company Genzyme to develop a host of new medicines for neglected diseases.¹⁰⁷ The Indian government has developed a range of incentives to encourage research into neglected diseases.¹⁰⁸ A partnership between the Indian Council of Science and Industrial Research and Indian pharmaceutical company Lupin has produced a promising molecule, Sudoterb, to combat tuberculosis.¹⁰⁹ Furthermore, companies from emerging economies are pursuing South-South co-operation for local production; for example, Brazil's Oswaldo Cruz Foundation¹¹⁰ is developing ARV-production sites in Mozambique. Companies are also engaging in PDPs: for example, Ranbaxy is a member of the Medicines for Malaria Venture (MMV).

Global solidarity for financing R&D

Global solidarity for R&D is essential to ensure that new medicines, vaccines, and diagnostics are produced to meet the needs of 90 per cent of the world's population. Increased and better aid is an important prerequisite for building a truly global system of R&D, but developing countries should also increase their contribution and scale up their own activities to

promote innovation for diseases relevant to their public-health needs. A global framework for R&D would ensure that these efforts to improve R&D were well co-ordinated.

There are various ideas that address the issue of global co-ordination and co-operation for meeting the health needs of developing countries. The Global R&D Treaty, proposed by eminent scientists and NGOs, would, first, set a 'norm' of countries' contributions to R&D so that sustainable financing of R&D was guaranteed. Each country would then decide the way in which it would honour its 'norm', whether via the patent system (by paying higher medicine prices) or by other means such as direct funding for R&D.¹¹¹ The treaty provides a novel approach for a global system and should be further explored by interested parties, including governments.¹¹²

The pharmaceutical industry introduced its own concept of a Global Fund for Neglected Diseases R&D.¹¹³ This fund would secure predictable and long-term financing for R&D projects that are carried out by PDPs, including clinical trials. It would also enable coherence and knowledge sharing between different projects. The Fund aims to base funding decisions on independent scientific criteria that would exclude politics from the decision-making process. Products would be made available at an inexpensive price in poor countries, including open licences, to foster generic competition.¹¹⁴

However, the industry proposal focuses only on financing product development through PDPs, and for a select group of neglected diseases. This proposal excludes diseases, formulations, and other research priorities that occur outside PDPs. While it would promote the development of new medicines, it would not resolve the broader trade-off between innovation and access. Although it would enable production of generic medicines to treat neglected diseases, it would preserve IP protection for other uses of the same product.¹¹⁵ In many cases, second uses of a product are highly relevant to the developing world. For example, if a Hepatitis C treatment were a secondary application of a potential new medicine to treat dengue fever, it would be patented and sold exclusively by the pharmaceutical industry. This could lead to a lack of access,

especially as poor countries have a high burden of Hepatitis C.¹¹⁶

Although the proposed Global Fund could play a positive role in improving R&D for poor-country diseases, there are other approaches to support innovation through a Global Fund. In 2001, Oxfam called for the creation of a US \$5 billion international fund under the auspices of the WHO to support research into new medicines and vaccines to treat infectious diseases plaguing poor countries. Capital under the fund would be provided by governments worldwide, in proportion to their means, giving all countries a stake. The fund would overcome the fragmentation of current research efforts, and allocation of resources would follow clearly defined public-health priorities.¹¹⁷

The fund, whose size would need to be re-calculated and assessed by all countries, could be modelled on the following principles.

- It should be part of a global R&D framework and would prioritise products for all diseases prevalent in developing countries.
- It should finance all relevant R&D within and outside PDPs, including basic science produced by public institutions or small companies.
- All countries would contribute according to their means, and therefore all would have a stake in the political decision-making process.
- Medicines, vaccines, and diagnostics that emerged from the Fund should be made available in all developing countries at affordable prices.
- There should be a clause on technology transfer in the funding agreement, so that the scientific expertise could extend beyond multinational pharmaceutical companies.

A global framework for health-driven innovation and access could also ensure that the needed compounds, know-how, and technology are accessible.

Guidelines for financing R&D

Underpinning a Global Fund and a global framework for R&D is the need for rich countries to spend money responsibly, systematically and effectively. In addition to making decisions on a sound scientific basis, donors should adhere to criteria set out in Box 7.

Box 7: Criteria for donor financing of R&D

- Transparent reporting of expenditures on R&D for diseases that predominantly affect developing countries. Declaration of actual R&D costs.
- Scientific data and outcomes should be shared in the public domain.
- Commitment to capacity building of research institutions, technology transfer, and development and best use of clinical-trial capacity to meet needs in the long term in developing countries.
- Affordable prices for resulting products.
- Equal voice for developing countries (governments and civil society) in decision-making processes at the global and national levels.
- Commitment to global co-ordination, including its financing.

The role of multilateral institutions

Apart from governments and industry, multilateral institutions have a part to play in R&D. Aside from its role to implement the Global Strategy and Plan of Action, WHO should evaluate and promote new models of innovation on the basis of evidence. Based on its global mandate to serve the interests of its member states, WHO is best suited to fill the co-ordination vacuum among the various financing and research institutions in order to ensure effective use of global resources. Other UN agencies, especially UNDP, UNCTAD, WIPO, UNIDO, and the World Bank, have key roles to play in sustaining and building interest in developing countries to promote R&D, in raising the necessary resources, and in compelling the development of a viable framework to co-ordinate various forms of R&D.¹¹⁸

9 Conclusion and recommendations

The lack of medical innovation is a global problem which requires a significant increase in resources, applied in an effective and co-ordinated manner. The current system of R&D under-utilises the capacities, skills, and resources available in all countries. Efforts to improve R&D across the developing world are fragmented, unsustainable, and unlikely to lead to large-scale changes.

In order to make improvements to the global system of innovation in a coordinated and effective manner, Oxfam makes the following recommendations.

1. The WHO, in collaboration with other multilateral agencies, should lead a concerted effort to establish a Global Fund for Research and Development of medicines. The Global Fund should be linked to a R&D framework. All countries should contribute to the Fund according to their GDP, and the philanthropic sector should also participate. All contributors should have a stake in setting priorities.
2. The R&D agenda of all countries, philanthropic foundations, the pharmaceutical industry, and product development partnerships should be set to include – in addition to discovery of new compounds and the development of new medicines – the adaptation of formulations suitable for developing country needs, and for population groups, including children and women.
3. New incentives for R&D, such as prize funds, which avoid patent pitfalls, or those that ensure IP is not a barrier to innovation, such as patent pools, should be implemented and evaluated by donors and developing countries with respect to their utility to meet particular needs. The TB prize fund and UNITAID patent pool serve as helpful models for further development of these and other creative mechanisms.
4. Donor governments should scale up their contributions to R&D for diseases predominantly affecting developing countries through official development assistance and their own research budgets. Developing countries should

prioritise R&D in their own budgets. All governments should coordinate their R&D efforts with universities, research institutions and private foundations through the R&D framework. This framework could mirror other initiatives that will rationalise health aid for developing countries, such as the International Health Partnership (IHP).

5. Donors, including private philanthropic foundations, should follow internationally agreed criteria when prioritising their financial contributions for R&D. They should commit to: transparency of information concerning the amount and nature of their contributions to R&D; open access to the data that is produced; building the capacity of academics and research institutions in developing countries; assistance for technology transfer; long-term planning for sustainable clinical-trial capacity in developing countries; involvement of developing country governments and civil society in decision making; and making the resulting products affordable, including through open licensing of emerging products
6. Pharmaceutical companies and universities should recognise the weaknesses of the IP system to respond to the need for new and adapted health products for the diseases of developing countries. They should support PDPs by providing expertise and access to compound libraries and continue to develop stand-alone or joint research centres tackling neglected diseases. They should cooperate in the early involvement of generic companies, biotechnology companies, and academia to devolve costs of parts of the R&D process, and to speed the delivery of effective new products.

Notes

¹ Commission on Health Research for Development, *Health Research: Essential Link to Equity in Development*, New York, Oxford University Press, 1990 (www.cohred.org).

² While the total global expenditure allocated to research relevant to all the health problems of developing countries is difficult to measure, studies by the Global Forum for Health Research and others 'demonstrate that health research applied to the needs of developing countries remains grossly under-resourced in many areas and the term '10/90 gap', while not representing a current quantitative measure, has become a symbol of the continuing mismatch between needs and investments'. See www.globalforumhealth.org for more information on the 10/90 gap.

³ Families USA, *Investing in Global Health Research: Neglected Tropical Diseases*, Washington: Families USA, 2007, p. 2. Available at <http://familiesusa.org/issues/global-health/global-health-neglected.pdf> (last accessed: October 2008).

⁴ It should be noted that neglected tropical diseases are only part of the problem. Neglected diseases are defined by WHO as those that 'affect almost exclusively poor and powerless people living in rural parts of low-income countries'. They include leishmaniasis, onchocerciasis, Chagas disease, leprosy, TB, schistosomiasis, lymphatic filariasis, sleeping sickness, and dengue fever. P. Hunt (2007) 'Neglected Diseases: A human rights analysis', World Health Organization. Available at: www.who.int/tdr/publications/publications/pdf/seb_topic6.pdf (last accessed October 2007). This paper addresses the health needs of developing countries with regard to so-called Types I, II, and III diseases. See Fn. 9.

⁵ P. Trouiller, P. Olliaro, E. Torreele, J. Orbinski, R. Laing, and N. Ford (2002) 'Drug development for neglected diseases: a deficient market and a public-health policy failure', *The Lancet* 359 (9324): 2188–94; for updated figures, see E. Torreele and P. Chirac (2005) 'Global framework on essential health R&D', *The Lancet* 367 (9522): 1560–1.

⁶ LDCs are exempt from providing patents on pharmaceuticals until 2016.

⁷ WHO: 'Public Health, Innovation and Intellectual Property Rights. Report of the Commission on Intellectual Property Rights, Innovation and Public Health', Geneva, 2006. Available at www.who.int/entity/intellectualproperty/report/en/index.html (last accessed October 2008).

⁸ One of the targets of the eighth MDG is 'in cooperation with pharmaceutical companies, [to] provide access to affordable essential drugs in developing countries'.

⁹ For instance, new reports indicate a rise in neglected diseases in Italy – such as increased cases of malaria and leishinimiasis, two diseases that are

well-known neglected diseases through sub-Saharan Africa, but virtually unknown in Western Europe until recent years. See 'Climate change brings malaria back to Italy', Guardian newspaper, www.guardian.co.uk/environment/2007/jan/06/italy.climatechange

Another disease that has grown more prevalent in Italy is chikungunya, a tropical virus for which there is no vaccine. See 'Mosquito virus arrives in Europe', BBC News at <http://news.bbc.co.uk/2/hi/health/6981476.stm>

¹⁰ 'Type II diseases are incident in both rich and poor countries, but with a substantial proportion of the cases in the poor countries. HIV/AIDS and tuberculosis are examples. ... Type III diseases are those that are overwhelmingly or exclusively incident in the developing countries, such as African sleeping sickness (trypanosomiasis) and African river blindness (onchocerciasis)' (WHO, 2006, *op. cit.*, fn. 7) However, Type I diseases, which occur in both rich and poor countries, such as measles or diabetes, often present research needs with regard to products that need to be adapted to the conditions of developing countries.

¹¹ See Oxfam Briefing Paper, 'Patents vs Patients: Five Years after the Doha Declaration', November 2006 at www.oxfamamerica.org/newsandpublications/publications/briefing_papers/patents_patients/Doha5_Final_paper_101106_2.pdf

¹² According to Moran *et al.*, pharmaceutical companies 'down-sized, spun-off or closed down infectious disease divisions that were insufficiently lucrative. This included companies like Roche, Bristol-Myers Squibb, Abbott, Eli Lilly and Wyeth, some of whom maintained programs only for those infectious diseases that provide a commercial benefit in rich countries, such as Hepatitis C and HIV.' See M. Moran, A. Ropars, J. Guzman, J. Diaz, C. Garrison: 'The New Landscape of Neglected Disease Drug Development', London School of Economics and Political Science/ Wellcome Trust: London, 2005, p. v.

¹³ A 'patent thicket' is a dense web of overlapping patents that can preclude a company from either developing or commercialising a new technology due to concerns over patent infringement.

¹⁴ See M. Heller (2008) 'Where Are the Cures: How patent gridlock is blocking the development of lifesaving drugs', *Forbes*, August 11, 2008 at www.forbes.com/forbes/2008/0811/030.html

See also C. Cookson (2008) 'Patent war hits life sciences', *Financial Times*, September 24, 2008 at www.ft.com/cms/s/0/fdff91e6-89d0-11dd-8371-0000779fd18c.html?nclick_check=1

See also: Birgit Verbeure, Esther van Zimmeren, Gert Matthijs, Geertrui Van Overwalle: 'Patent pools and diagnostic testing', *TRENDS in Biotechnology*, Vol. 24, No. 3, March 2006.

¹⁵ Instead of promoting true innovation, pharmaceutical companies, due in part to the perverse incentives created by IP rules, have instead sought extensions on pharmaceutical patents (ever-greening), to pursue only blockbuster returns on medicines and to develop 'me-too' medicines in lieu of true innovation. [0]

¹⁶ The most commonly known statistic is that between 1975 and 1997 only 13 new medicines or vaccines addressing neglected diseases emerged from public and private R&D efforts. Furthermore, from 1999 to 2004, only an additional three medicines emerged. Cf. P. Trouiller, P. Olliaro, E. Torreele, J. Orbinski, R. Laing, and N. Ford (2002) 'Drug development for neglected diseases: a deficient market and a public-health policy failure', *The Lancet* 359 (9324): 2188–94; for updated figures see E. Torreele and P. Chirac (2005) 'Global framework on essential health R&D', *The Lancet* 367 (9522): 1560–1.

¹⁷ Infectious diseases kill 11 million people every year globally, and nearly all deaths occur in low and middle-income countries. Three infectious diseases in particular kill the most people in the developing world – HIV and AIDS, TB, and lower respiratory infections. Infectious diseases are particularly likely to kill children in poor countries. According to WHO statistics, seven of the top ten causes of death in children in low and middle-income countries are due to infectious diseases, accounting for 6.5 million deaths every year. See: www.dcp2.org/file/6/DCPP-InfectiousDiseases.pdf

¹⁸ Neglected tropical diseases are a subset of all neglected diseases. They are generally known as Type III diseases, which are those diseases that are overwhelmingly or exclusively incident in developing countries, such as African sleeping sickness (trypanosomiasis) and African river blindness (onchocerciasis). The WHO notes that the following are generally known as tropical neglected diseases, or African trypanosomiasis, Chagas disease, Dengue fever, Leishmaniasis, Leprosy, Lymphatic filariasis, Malaria, Onchocerciasis, Schistosomiasis and tuberculosis.

¹⁹ See www.who.int/tdr/diseases/default.htm World Health Organization (WHO), *Neglected Tropical Diseases: Hidden Successes, Emerging Opportunities* (Geneva: WHO, 2006).

²⁰ 'Drug development for maternal health cannot be left to the whims of the market', The PLoS Medicine Editors, *S Med* 5(6): e140 doi:10.1371/journal.pmed.0050140, June 24, 2008

²¹ There were 9.2 million new TB cases in 2006. See www.who.int/tb/publications/2008/factsheet_april08.pdf for more information.

²² M. A. Aziz, A. Wright, A. Laszlo, A. De Muynck, F. Portaels, A. Van Deun, C. Wells, P. Nunn, L. Blanc, and M. Raviglione, for the WHO/International Union Against Tuberculosis And Lung Disease Global Project on Anti-tuberculosis Drug Resistance Surveillance (2006): 'Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis', *The Lancet* 368 (9553): 2142–54.

²³ For example, see: www.usaid.gov/our_work/global_health/id/tuberculosis/techareas/tbhiv.html Furthermore, the existing TB vaccine, when administered to a HIV-positive baby, can cause a HIV-positive infant to develop TB due to the weakened immune system. See www.newscientist.com/channel/health/hiv/dn12871-tb-vaccine-poses-threat-to-hivpositive-babies.html

²⁴ Global Alliance for TB Drug Development (TB Alliance): *Pathway to Patients. Charting the Dynamics of the Global TB Drug Market*, 2007.

Available at:

www.tballiance.org/downloads/publications/Pathway_to_Patients_Overview_FINAL.pdf

²⁵ Médecins Sans Frontières – Campaign for Access to Essential Medicines: ‘Putting Patients’ Needs First: New Directions in Medical Innovations’, 2008.

²⁶ This figure is based on estimates by an expert within WHO in a draft paper estimating off-label uses of medicines. As a result, treatment is often ‘off-label’, resulting in under- and over-dosing, with potential harms. Diseases such as HIV and TB require taking more than one medicine, sometimes more than once a day. Therefore fixed-dose combinations of medicines are often the only practical means of administration. Children may suffer from more than one disease, compounded by underlying vulnerabilities from malnutrition and parasites.

²⁷ See www.who.int/phi/en/

²⁸ ‘Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property’, WHA 61.21, 24.05.2008. Available at

www.who.int/gb/ebwha/pdf_files/A61/A61_R21-en.pdf

The strategy recognises IP as a key feature, but it also calls upon the WHO, and all countries, to identify new means to deliver innovation, while also applying existing technologies to the essential health needs of the poor.

²⁹ H. Mintzberg, ‘Patent nonsense: evidence tells of an industry out of social control’, *Canadian Medical Association Journal* 175 (4), 15 August 2006, www.cmaj.ca/cgi/content/full/175/4/374

³⁰ The European Commission, according to Oxfam’s research, is providing 450 million Euros to address TB, HIV and AIDS, and malaria, and a mere 45 million Euros to address all other neglected diseases.

³¹ According to the International Federation of Pharmaceutical Manufacturers Association (IFPMA), approximately US\$ 10.3 billion will be needed over the next decade to drive forward and complete product development. However, this figure has not been substantiated by any independent third party and may reflect inflated R&D estimates.

³² For example, the European Union recently announced a new funding stream, the Innovative Medicines Initiative (IMI), which will provide US\$ 2 billion over a seven-year period to support R&D, in co-ordination with the pharmaceutical industry, for a range of rich-country diseases. This sum far exceeds the estimated 1.4 billion dollars spent by all PDPs through public and private funds since their inception in 1996.³² While new medicines are needed in rich countries, the stunning lack of effective medicines for diseases prevalent in developing countries means that poor patients continue to suffer unnecessarily. See Andrew Jack: ‘EC nears deal with drug makers’, *Financial Times*, 20 December 2007.

³³ Greater links between universities and public institutions with pharmaceutical companies create concerns that new compounds, research tools, and scientific knowledge will be unavailable in the public domain,

thereby limiting the scope of scientific innovation to narrow commercial needs. Universities themselves are increasingly unwilling to share IP in the public interest, in spite of their respective mandates, viewing IP solely as a source of commercial profit via technology transfer. Some observers now call universities 'patent trolls'. See M. Lemley (2007) 'Are Universities Patent Trolls?', Stanford Public Law Working Paper No. 980776_at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=980776, April 11, 2007.

³⁴ See www.vaccineamc.org/files/AMC_FactSheet_v2.pdf

³⁵ T. Von Schoen Angerer (2008) 'Questioning the 1.5 billion dollar vaccine deal', *Development Today*, April 25 2008.

³⁶ Recently, the United States enacted legislation which directs the US government to explore financing for a future AMC to develop a vaccine that addresses HIV and AIDS, malaria, TB or 'other related infectious diseases'.

³⁷ The scheme requires the producing pharmaceutical companies to offer the vaccine at a set target price until the subsidy runs out, and then to offer the vaccine at a lower 'tail price' for an additional period.

³⁸ Three products are now on the market and several more are in late-stage clinical trials. The three PDP drugs that have been registered as of the writing of this report are: paramomycin intramuscular injection (IM) for visceral leishmaniasis [Institute for OneWorld Health, IoWH], artesunate+amodiaquine fixed-dose combination (FDC) for malaria [Drugs for Neglected Diseases Initiative, DNDi], and artesunate+mefloquine FDC for malaria [DNDi].

³⁹ See WHO 2006, pp. 75–76, *op. cit.*, fn. 7. Also R. Widdus and K. White (2004) 'Combating Diseases Associated with Poverty: financing strategies for product development and the potential role of public–private partnerships', Initiative for Public–Private Partnerships for Health, 2004. Available at www.globalforumhealth.org/filesupld/ippph_cd/06.PDF

⁴⁰ Two products that have emerged from PDP pipelines have not been patented: the anti-malarial medicine ASAQ (developed by DNDi) and paromyocin.

⁴¹ Oxfam-commissioned research shows that PDPs are more likely to gain control over IP if they are involved from the early stages or have paid for a significant proportion of development costs.

⁴² Prices offered to the poorest in MICs must be comparable to those prices offered to LDCs.

⁴³ Section 2.4b of the WHO Global Strategy from the Inter-Governmental Working Group calls for 'promoting greater access to knowledge and technology relevant to meet public health needs of developing countries', especially to 'promote public access to the results of government-funded research by strongly encouraging that all investigators funded by governments submit to an open access database an electronic version of their final, peer-reviewed manuscripts'. Rich-country governments can, for example, establish publicly accessible databases of scientific data. Two

initiatives that have encouraged greater access to scientific literature and data are the NIH Pubmed Central and the Wellcome Trust Initiatives.

⁴⁴ Greater access to private-sector and university compound libraries is an element of the new WHO Global Strategy and Plan of Action.

⁴⁵ Oxfam-commissioned research on Product Development Partnerships, Suerie Moon, August 2008.

⁴⁶ The priority review voucher was introduced as a Neglected Diseases Amendment to the Food and Drug Administration Revitalization Act. The relevant legislative language can be found at: www.fda.gov/oc/initiatives/HR3580.pdf (pages 151-153 of the PDF)

⁴⁷ The voucher can also be sold to third parties.

⁴⁸ PRVs effectively increase patent life, even though it does not increase the patent term.

⁴⁹ Although a PDP does not develop and market medicines that are targeted at rich country markets, the voucher is fully transferable to any third party (a multinational pharmaceutical company) who can pay a fixed sum for the voucher.

⁵⁰ See M. Moran, A. Ropars, J. Guzman, J. Diaz, and C. Garrison (2005) 'The new landscape of neglected disease drug development' London School of Economics and Political Science; Wellcome Trust: London, 2005. Available at: www.wellcome.ac.uk/stellent/groups/corporatesite/@msh_publishing_group/documents/web_document/wtx026592.pdf (Last accessed: Oct. 2008)

⁵¹ This was proposed in a separate piece of legislation that would have introduced a tax credit for neglected-disease drug development. See Senate Bill No. 2351 (110th Congress), or 'A bill to amend the Internal Revenue Code of 1986 to provide a tax credit for medical research related to developing infectious disease products' introduced on November 14, 2007 entitled.

⁵² The WHO Global Strategy and Plan of Action, under Section 2.4d, calls upon countries to encourage the further development and dissemination of publicly funded or donor-funded medical inventions and know-how through appropriate licensing policies, including but not limited to open licensing, that enhance access to innovations for development of products of relevance to the public-health needs of developing countries on reasonable, affordable, and non-discriminatory terms.

⁵³ Novartis, in response to Oxfam's inquiry about submitting Coartem for FDA approval, stated: '[...] Novartis is pursuing FDA approval. Please note that [Novartis'] decision to submit a US NDA for Coartem, an ACT, was made prior to enactment of the PRV law and was, in part, prompted by patients' needs and encouragement from the FDA.' 'As [Novartis] have not discussed with FDA whether Coartem qualifies for the voucher program, [Novartis] do not know if it qualifies but assume it would – if approved.' 'Coartem is one of the advances in malaria treatment which has delivered massive health benefit. Since 2001, [Novartis] have provided more than 200

million treatment courses, which have helped save an estimated 500k lives. In order to achieve this, the company has taken massive risk and investments for development and scaling up – at no profit. Incentives like the PRV will encourage other companies to undertake similar initiatives and facilitate future engagement of Novartis in other disease areas.’ Email correspondence from Novartis to Oxfam International on October 14, 2008.

⁵⁴ In the USA, the Orphan Drug Act is granted for a medicine that addresses a disease affecting fewer than 200,000 people.

⁵⁵ WHO, 2006, pp. 86-87, *op. cit.*, fn. 7.

⁵⁶ Cf. T.J. Tucker and M. Makgoba: ‘Public-private partnerships and scientific imperialism’, *Science*, Vol. 320, 23 May 2008, pp. 1016-17.

⁵⁷ The European Commission is attempting to move forward in this regard: in November 2008 it will hold a conference entitled ‘Challenges for the Future – Research on HIV/AIDS, Malaria and TB’ in order to identify research gaps and help with funding prioritisation. See <http://poverty-related-diseases.teamwork.fr/?page=intro&type=>

⁵⁸ In the USA, for example, spending on neglected diseases resides in a variety of agencies and departments, including the NIH, Centers for Disease Control, the Fogarty Institute, USAID, the Department of Defense, and the NIAID. Multiple research centres and development agencies are relied upon in Canada and the European Union.

⁵⁹ Both have caused thousands of deaths over the past four decades, due to sporadic outbreaks in poor countries. Ebola is highly infectious, and the world should be prepared for another outbreak in order to avoid more deaths.

⁶⁰ Internal Oxfam research, Johanna von Braun. Interview with Ole Olesen – DG Research of the European Union, Neglected Diseases Unit.

⁶¹ New and adapted antibiotics, for example, come into this category. Pipelines are generally thought to be dry, yet resistant organisms continue to evolve, posing high risks to public health. Pneumonia, neonatal sepsis, maternal sepsis, and many opportunistic infections require the availability of effective antibiotics.

⁶² See www.internationalhealthpartnership.net and www.cbd.int/chm/ for more information. National focal points of the Clearing House Mechanism provide, among other things, information about available technologies. They could be extended to co-ordinate funding schemes at the national level.

⁶³ Other types of co-ordination need to be implemented. For example, a single agency could keep records of where money was spent on building new clinical-trial sites, so that other drug developers, including PDPs, could make use of it. When chemical compounds are already rejected during screening, other researchers need to know, so that efforts are not duplicated.

⁶⁴ Knowledge Ecology International: ‘IGWG Submission on Collective Management of Intellectual Property – The Use of Patent Pools to Expand Access to Needed Medical Technologies’, 30 September 2007. Available at

www.who.int/phi/public_hearings/second/contributions_section2/Section2_ManonRess-PatentPool.pdf

⁶⁵ A similar practice is quite common in the field of information technology.

⁶⁶ In discussions with NGOs and at public meetings (especially at the World AIDS Conference), three multinational companies, Gilead Sciences, Johnson and Johnson, and Merck have indicated tentative support for the patent pool. Glaxo Smith Kline has issued a policy supporting the use of patent pools 'in principle'.

⁶⁷ See www.innocentive.com

⁶⁸ See S.2210 the Medical Innovation Prize Fund Act of 2007, first introduced in 2005 as H.R. 417. Available at: www.keionline.org/misc-docs/Prizes/experts_on_s2210.pdf

⁶⁹ Participation would be voluntary. One criticism of the idea of prize funds is that it would be difficult to measure the actual health impacts and to offer appropriate prizes tailored to those impacts. Thus, some experts prefer to first offer individual prizes to assess the efficacy of the system and to improve measurement. It should be noted that some countries, such as Canada and Australia, have at least developed methodologies to measure the health impact of new medicines that are launched on their market, and especially the therapeutic significance of the medicine compared with already existing interventions.

⁷⁰ Bolivia and Barbados submitted five different prize proposals to encourage development of new medicines to treat several diseases. See www.keionline.org/index.php?option=com_content&task=view&id=4 for the proposals.

⁷¹ 'Working Document – Barbados and Bolivia. Proposal 1: Prize Fund for Development of Low-Cost Rapid Diagnostic Test for Tuberculosis.' Available at www.keionline.org/misc-docs/b_b_igwg/prop1_tb_prize.pdf The prizes would be administered by representatives from various multilateral organisations and national public institutions, and paid for by governments or through other forms of financing.

The TB prize as currently advocated by Knowledge Ecology International, MSF and others also has an important open source/access component that basically includes several incentives to promote collaboration and access to knowledge. For example, part of the prize would be given to unaffiliated and uncompensated (by the winning entrant) scientists and engineers that openly published and shared research, data materials and technology, on the basis of who provided the most useful external contributions to achieving the end result.

⁷² Recently the WHO, the Stop TB Partnership, UNITAID, and the Foundation for Innovative New Diagnostics (FIND) announced an initiative that will see rapid, new molecular tests to diagnose MDR-TB in less than two days introduced in 16 countries over the next four years. Cf.: 'Rapid Tests for Drug-resistant TB to be Available in Developing Countries', 30 June 2008. Available at www.who.int/tb/features_archive/mdrtb_rapid_tests/en/ (last accessed: October 2008).

⁷³ A licensing agency would be created for acquiring needed rights for the relevant patents, data and know-how for the diagnostic test – the TB Licensing Agency (TBLA).

⁷⁴ At least half of the 'best contributions' prize money would be set aside for research teams working in developing countries.

⁷⁵ See www.yale.edu/macmillan/igh/ for more information and to download A. Hollis, T. Pogge (2008) 'The Health Impact Fund. Making New Medicines Accessible for All', *Incentives for Global Health*, 2008.

⁷⁶ The authors of the 'Health Impact Fund'-proposal have stipulated US\$6 billion as a possible annual amount to be funded by governments and donors, although this can be extended in the future if the up-take of the Health Impact Fund increases considerably.

⁷⁷ Hollis/Pogge (2008) p. 1, *op. cit.*

⁷⁸ There are concerns that the near marginal cost of medicines (determined by the HIF on the basis of data submitted by the innovator company) would be higher than under conditions of free generic competition. Also, due to the limitations of competition, prices could be higher because of limited economies of scale. For a critic of the monopoly supply model see: Jamie Love. *Open licensing vs Monopoly Controlled Supply*. Available at: www.keionline.org/index.php?option=com_jd-wp&Itemid=39&p=112

⁷⁹ However, it should be noted that some countries, such as Canada and Australia, have at least developed methodologies to measure the health impact of new medicines that are launched on their market, and especially the therapeutic significance of the medicine compared with already existing interventions.

⁸⁰ Oxfam has stipulated that aid must be predictable, long-term, and, where possible, given to poor-country government budgets or the health sector to help them to build and maintain national development and to allow for ownership of scientific policy according to their needs. Aid must not be made conditional on the purchase of rich-country goods or services, or require poor countries to implement specific economic policies. Finally, aid should be given in a transparent and accountable manner.

⁸¹ Currently only Germany is supporting local production in a few countries.

⁸² S. J. Haakonsson (2008) 'Governance and Upgrading in the Global Value Chain for Pharmaceuticals. With Case Studies on Uganda and India', unpublished PhD Thesis, Department of Geography, University of Copenhagen.

⁸³ GTZ (2007) 'The Viability of Local Pharmaceutical Production in Tanzania', Eschborn, 2007, pp. 43-44. Available at: www.gtz.de/en/themen/laendliche-entwicklung/13421.htm (Last accessed: Oct. 2008)

⁸⁴ A. T. Kearney (2006) 'Make Your Move: Taking Clinical Trials to the Best Location', available at www.atkearney.com

⁸⁵ K.S. Jayaraman: 'Outsourcing clinical trials to India rash and risky, critics warn', *Nature Medicine*, Vol. 10, No. 5 (May 2004), p. 440.

⁸⁶ According to Jayaraman (*ibid.*), however, 'the US Food and Drug Administration does not approve data from trials in which more than 20% of subjects are from developing countries'.

⁸⁷ 'In 2005, the industry for clinical trials in India was US\$ 100 million.' See The Associated Chambers of Commerce and Industry of India: 'White Paper on Indian Pharma Industry Quest for Global Leadership', 2006. Available at www.cygnusindia.com/Articles/Indian_Pharma_Industry_Quest_for_Global_Leadership-09.11.pdf

⁸⁸ Sally Ellis: 'Operational challenges: clinical trial partnerships in Africa', *DNDi Newsletter*, June 2008, www.dndi.org/newsletters/16/4_1.html

⁸⁹ However, a recent study indicates that there is sufficient capacity in sub-Saharan Africa to test the new pipeline of medicines to treat malaria. See Moran et al, 'Clinical Trial site capacity for malaria drug development', *Health Partnerships Review*, Global Forum for Health Research at www.globalforumhealth.org/filesupld/hpr/HealthPartnershipsReview_Full.pdf

⁹⁰ Piero O. Olliaro and Steven C. Wayling: 'Facing dual challenge of developing both products and research capacities for neglected diseases', *Global Forum for Health Research: Health Partnerships Review. Focusing collaborative efforts on research and innovation for the health of the poor*. Available at www.globalforumhealth.org/filesupld/hpr/HealthPartnershipsReview_Full.pdf

⁹¹ For example, for clinical trials of treatments for sleeping sickness and visceral leishmaniasis the diagnosis has to be confirmed 'through invasive procedures such as lumbar punctures or splenic aspirates necessary to detect the parasite, as more readily field-adapted diagnostics are not yet available' (Ellis, *op. cit.*, fn. 9).

⁹² If a medicine is successful in trials and hence approved for the market, participants in clinical trials must continue to receive treatment at no cost, as they help to make the drug available to patients in both developed and developing countries. More broadly, pharmaceutical firms that secure lower costs and faster approval times should reduce medicine prices in line with the lower drug-development costs and higher profits that emerge. This is especially valid for clinical trials for Type I diseases.

⁹³ Olliaro and Wayling, *op. cit.*, fn. 10.

⁹⁴ The USA is investing more in clinical-trial capacity in developing countries – especially through the PEPFAR (President's Emergency Plan for AIDS Relief) Reauthorisation Bill. It identifies USAID as an agency authorised to use public–private partnerships for the strengthening of institutions in developing countries, for reviewing protocols for clinical trials, and to improve the implementation.

⁹⁵ See www.edctp.org

⁹⁶ Naomi Antony: 'Clinical Trials in Africa Receive Funding Boost', 6 June 2008. Available at: www.scidev.net/en/health/malaria/news/clinical-trials-in-africa-receive-funding-boost.html

⁹⁷ The US Army runs a Medical Research Project in Kisumu, Kenya, (USAMRU-K), which conducts applied medical research in malaria, leishmaniasis, and arboviruses. More recently, USAMRU-K has been involved with surveillance for both avian and pandemic influenza and has built other surveillance sites in Cameroon and Uganda. See http://books.nap.edu/openbook.php?record_id=11974&page=123

⁹⁸ See www.fic.nih.gov

⁹⁹ 21 February 2008. See www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P6-TA-2008-0067+0+DOC+XML+V0//EN&language=EN

¹⁰⁰ See also Oxfam International: 'Investing for Life: Meeting Poor People's Needs for Access to Medicines through Responsible Business Practices', 2007. Available at www.oxfam.org/files/bp109-investing-for-life-0711.pdf

¹⁰¹ See IMS Health, World Pharmaceutical Market Summary (2008)

¹⁰² In the USA, neglected diseases disproportionately affect women and children. Geographically, they predominantly occur within inner cities, in the Mississippi Delta, Apalachia, and along the Mexican border. See Steve Sternberg: 'US poor are vulnerable to neglected diseases', *USA Today*, 25 June 2008.

¹⁰³ See P. Engardio and A. Weintraub (2008) 'Outsourcing the Drug Industry', *Business Week*, September 4, 2008 at: www.businessweek.com/magazine/content/08_37/b4099048471329.htm

¹⁰⁴ 'Brazil discovers new ARV candidates', *Scrip World Pharmaceutical News*, No 3394, 4 September 2008.

¹⁰⁵ WHO, 2006, p. 145, *op. cit.*, Fn. 7.

¹⁰⁶ Two other major manufacturing sites of the DPT vaccine are South Korea and Brazil.

¹⁰⁷ Genzyme press release, 'Oswaldo Cruz Foundation and Genzyme Form Collaboration to Advance New Drugs for Neglected Diseases', www.genzyme.com/corp/media/GENZ%20PR-072307.asp

¹⁰⁸ Oxfam-commissioned research found incentives including financing for clinical trials, direct financial support of public-private partnerships, and soft loans.

¹⁰⁹ However, Lupin filed for IP rights in India and the USA, thus harming access to the resulting medicine. See [www.csir.res.in/External/Utilities/Frames/collaborations/main_page.asp?a=opframe.htm&b=leftcon.htm&c=../../Heads/collaborations/Nmitli.htm](http://www.csir.res.in/External/Utilities/Frames/collaborations/main_page.asp?a=topframe.htm&b=leftcon.htm&c=../../Heads/collaborations/Nmitli.htm)

¹¹⁰ See www.fiocruz.br

¹¹¹ T. Hubbard and J. Love (2004) 'A new trade framework for global healthcare R&D', *PLoS Biology*, Vol. 2, No. 2, February 2004, pp. 0147-

0150. Available at <http://biology.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pbio.0020052> (last accessed October 2008).

¹¹² Rather than rational and genuine exploration of the Treaty's potential and challenges, it has faced enormous criticism not only from the pharmaceutical industry itself but also from industry-funded academics.

¹¹³ The Neglected Diseases R&D Fund was first introduced by members of the multinational pharmaceutical industry in November 2007 at a meeting of the WHO IGWG. Subsequent presentations have been made at various conferences, meetings and workshops.

¹¹⁴ This information was provided to Oxfam during a meeting hosted by Novartis at the World Health Assembly.

¹¹⁵ Pharmaceutical companies benefiting from research and scientific data that emerged from the Fund's research for neglected-diseases medicines would pay for using such data for other purposes. [0]

¹¹⁶ An estimated 31.9 million people are infected with Hepatitis C in Africa alone, and 170 million worldwide. See www.who.int/mediacentre/factsheets/fs164/en/ for more information

¹¹⁷ Oxfam Great Britain: 'Fatal Side Effects: Medicine Patents under the Microscope', 2001. Available at www.oxfam.org.uk/resources/policy/health/downloads/fatal_side_effects.rtf (last accessed October 2008).

¹¹⁸ These agencies should also pursue an internal assessment of how they could best provide inputs to the implementation of the Global Strategy and Plan of Action.

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<p>Oxfam America 226 Causeway Street, 5th Floor Boston, MA 02114-2206, USA +1 617 482 1211 (Toll-free 1 800 77 OXFAM) E-mail: info@oxfamamerica.org www.oxfamamerica.org</p>	<p>Oxfam Hong Kong 17/F., China United Centre, 28 Marble Road, North Point, Hong Kong Tel: +852 2520 2525 E-mail: info@oxfam.org.hk www.oxfam.org.hk</p>
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<p>Oxfam-in-Belgium Rue des Quatre Vents 60, 1080 Brussels, Belgium Tel: +32 2 501 6700 E-mail: oxfamsol@oxfamsol.be www.oxfamsol.be</p>	<p>Oxfam Ireland Dublin Office, 9 Burgh Quay, Dublin 2, Ireland Tel: +353 1 635 0422 Belfast Office, 115 North St, Belfast BT1 1ND, UK Tel: +44 28 9023 0220 E-mail: communications@oxfamireland.org www.oxfamireland.org</p>
<p>Oxfam Canada 250 City Centre Ave, Suite 400, Ottawa, Ontario, K1R 6K7, Canada Tel: +1 613 237 5236 E-mail: info@oxfam.ca www.oxfam.ca</p>	<p>Oxfam New Zealand PO Box 68357, Auckland 1145, New Zealand Tel: +64 9 355 6500 (Toll-free 0800 400 666) E-mail: oxfam@oxfam.org.nz www.oxfam.org.nz</p>
<p>Oxfam France – Agir ici 104 rue Oberkampf, 75011 Paris, France Tel: + 33 1 56 98 24 40. E-mail: info@oxfamfrance.org www.oxfamfrance.org</p>	<p>Oxfam Novib (Netherlands) Mauritskade 9, Postbus 30919, 2500 GX, The Hague, The Netherlands Tel: +31 70 342 1621 E-mail: info@oxfamnovib.nl www.oxfamnovib.nl</p>
<p>Oxfam Germany Greifswalder Str. 33a, 10405 Berlin, Germany Tel: +49 30 428 50621 E-mail: info@oxfam.de www.oxfam.de</p>	<p>Oxfam Québec 2330 rue Notre Dame Ouest, bureau 200, Montreal, Quebec, H3J 2Y2, Canada Tel: +1 514 937 1614 E-mail: info@oxfam.qc.ca www.oxfam.qc.ca</p>
<p>Oxfam GB Oxfam House, John Smith Drive, Cowley, Oxford, OX4 2JY, UK Tel: +44 1865 473727 E-mail: enquiries@oxfam.org.uk www.oxfam.org.uk</p>	

Oxfam International Secretariat: Suite 20, 266 Banbury Road, Oxford, OX2 7DL, UK
Tel: +44 1865 339100 Email: information@oxfaminternational.org. Web site: www.oxfam.org

Oxfam International advocacy offices:

E-mail: advocacy@oxfaminternational.org

Washington: 1100 15th St., NW, Ste. 600, Washington, DC 20005-1759, USA

Tel: +1 202 496 1170.

Brussels: Rue Philippe le Bon 15, 1000 Brussels, Belgium

Tel: +322 502 1941

Geneva: 15 rue des Savoises, 1205 Geneva, Switzerland

Tel: +41 22 321 2371.

New York: 355 Lexington Avenue, 3rd Floor, New York, NY 10017, USA

Tel: +1 212 687 2091.

Linked Oxfam organisations. The following organisations are linked to Oxfam International:

Oxfam Japan Maruko bldg. 2F, 1-20-6, Higashi-Ueno, Taito-ku, Tokyo 110-0015, Japan

Tel: + 81 3 3834 1556. E-mail: info@oxfam.jp Web site: www.oxfam.jp

Oxfam India - 2nd floor, Plot No.1, Community Centre (Sujan Mohinder Hospital), New Delhi,

India, tel: +91 (0) 11 4653 8000, fax: +91 (0) 11 4653 8099, email: delhi@oxfamindia.org,

website: www.oxfamindia.org

Oxfam International and Ucodep Campaign Office

Via Masaccio, 6/A 52100 Arezzo, Italy

Tel +39 0575 907826, Fax +39 0575 909819

email: ucodep-oi@oxfaminternational.org

Oxfam observer member. The following organisation is currently an observer member of Oxfam International, working towards possible full affiliation:

Fundación Rostros y Voces (México) Alabama 105, Colonia Napoles, Delegacion Benito Juarez, C.P. 03810 Mexico, D.F.

Tel: + 52 5687 3002 / 5687 3203 Fax: +52 5687 3002 ext. 103

E-mail: comunicación@rostrosyvoces.org

Web site: www.rostrosyvoces.org