Drugs for neglected diseases: a failure of the market and a public health failure?

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Drugs for neglected diseases: a failure of the market and a public health failure?

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Summary Infectious diseases cause the suffering of hundreds of millions of people, especially in tropical and subtropical areas. Effective, affordable and easy-to-use medicines to fight these diseases are nearly absent. Although science and technology are sufficiently advanced to provide the necessary medicines, very few new drugs are being developed. However, drug discovery is not the major bottleneck. Today's R&D-based pharmaceutical industry is reluctant to invest in the development of drugs to treat the major diseases of the poor, because return on investment cannot be guaranteed. With national and international politics supporting a free market-based world order, financial opportunities rather than global health needs guide the direction of new drug development. Can we accept that the dearth of effective drugs for diseases that mainly affect the poor is simply the sad but inevitable consequence of a global market economy? Or is it a massive public health failure, and a failure to direct economic development for the benefit of society? An urgent reorientation of priorities in drug development and health policy is needed. The pharmaceutical industry must contribute to this effort, but national and international policies need to direct the global economy to address the true health needs of society. This requires political will, a strong commitment to prioritize health considerations over economic interests, and the enforcement of regulations and other mechanisms to stimulate essential drug development. New and creative strategies involving both the public and the private sector are needed to ensure that affordable medicines for today's neglected diseases are developed. Priority action areas include advocating an essential medicines R&D agenda, capacity-building in and technology transfer to developing countries, elaborating an adapted legal and regulatory framework, prioritizing funding for essential drug development and securing availability, accessibility, distribution and rational use of these drugs.

keywords neglected diseases, medicines, pharmaceutical market, public policy

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Introduction

Infectious diseases kill 14 million people each year. More than 90% of these deaths occur in developing countries (WHO 1999). In addition to the HIV/AIDS pandemic, respiratory infections, malaria and tuberculosis are the leading causes of death and morbidity in Africa, Asia and South America – accounting for four-fifths of the world's population. Access to treatment for these diseases is problematic because medicines are unaffordable, have become ineffective, or are not adapted to local conditions of use. For several other diseases common in the developing world, medicines are simply non-existent.

Advances in scientific research have led to a greater understanding of the molecular and cellular basis of life, and this has resulted in increasingly sophisticated therapeutic strategies to cure a wide variety of diseases, including lifestyle diseases such as obesity and impotence. In contrast, despite the enormous burden of disease in poor countries, drug discovery and development targeted at tropical diseases has ground to a standstill (Pécoul *et al.* 1999). Only a small fraction of the total worldwide expenditure on health research and development (estimated at US$50–60 billion a year) is devoted to the development of such medicines (Global Forum for Health Research 1999). With the emergence of a free market-based world order, profit prospects rather than global health needs guide the direction of new drug development. The adverse public health consequences of this evolution for the tropical world have been grave (Trouiller 1996).

This paper first discusses the key factors that deter the pharmaceutical industry from conducting research and development (R&D) into these Neglected Diseases and then outlines possible new strategies and approaches to ensure that new and affordable medicines could be developed.

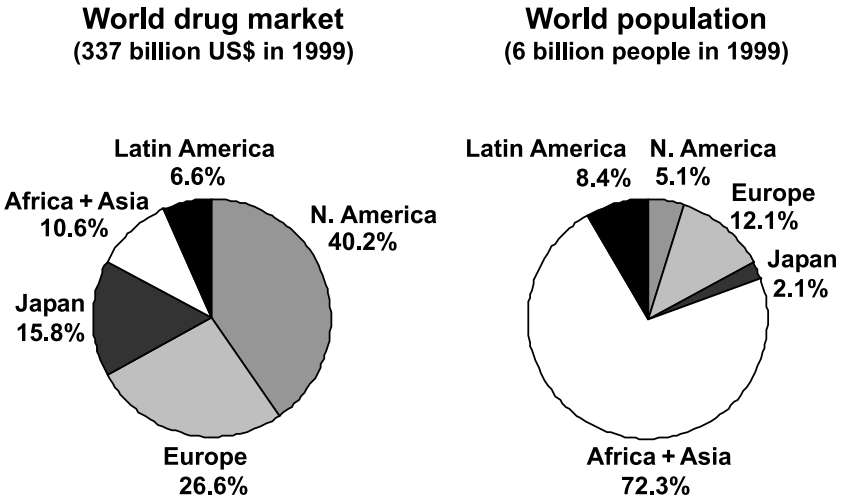
Priority setting in drug development

Drug development is a complex, expensive and time-consuming activity, subject to stringent regulations. Today, drug development is confined almost exclusively to a consolidated and highly competitive multinational drug industry driven by profit and subject to the laws of a globalized market economy. Market forces inevitably skew the direction of drug R&D towards those diseases and patients (customers) that assure the highest financial returns (Sachs 1999). In 1999, North America, Europe and Japan accounted for 82.4% of the world pharmaceutical market (valued at US$ 337 billion), while Africa and Asia, representing more than two-thirds of the world population, only accounted for 10.6% of the market (Figure 1) (IMS 1999). Despite the global public health relevance of infectious diseases, their predominant distribution in poor countries is perceived as a major disincentive to invest in the discovery and development of new treatments for these illnesses. Indeed, less than 1% of the 1223 new medicines launched on the international market between 1975 and 1997 were destined specifically for tropical communicable diseases (Trouiller & Olliaro 1999). These appalling statistics illustrate why these diseases, which include major killers such as malaria, justifiably warrant the term 'Neglected Diseases'.

Current barriers to drug development for neglected diseases

Costs of R&D

The most frequently voiced argument to explain or justify the pharmaceutical industry's near-zero investment in drugs for tropical infectious diseases is the high



Sources: IMS-Health 1999 / UNDP, World population 1998

Figure 1 Pharmaceutical market distribution compared to world population distribution.

development cost compared with the small expected financial return. The estimates of the true costs of R&D, however, remain highly controversial. In one study, the full after-tax cost of developing a new drug was estimated by the US Office of Technology Assessment at approximately US$ 312 million (in 1997 dollars) (Kettler 1999). Other estimates range between US$ 160 and 450 million (DiMasi *et al.* 1994; Grabowsky & Vernon 1994). These estimates are based on average costs (i.e. the total cost of all R&D, including failures, divided by the number of products introduced) and they are often challenged because they include running costs, overheads, spill-over and inefficiency. The cost of developing one specific product may be significantly lower – probably US$30–50 million (Love 1997). Moreover, quite often a substantial part of the financing of R&D for important medications comes from public sources (Attaran 1999).

Today, the pharmaceutical industry is amongst the most profitable industrial sectors (Fortune 500 2001), indicating that the high R&D cost does not necessarily constitute a barrier for significant returns on investment (O'Brien 1998). Moreover, large companies tend to spend at least as much on marketing and publicity as they spend on R&D (Gambardella *et al.* 2001). Meanwhile, however, the commercial targets of the R&D-based drug industry have risen to an ambitious minimum of US$ 200–300 million sales per developed drug per year. Smaller potential returns are considered as simply not worth the investment. Thus the only companies that can afford to invest in R&D have drifted away from tropical diseases.

Regulatory barriers

The increasingly strict and complex regulations that govern the development and sale of new drugs contribute to the high cost and time-consuming nature (8–12 years) of drug development. While a strong regulatory framework is necessary to protect the health of citizens, regulatory excesses may inhibit access to drugs, especially for neglected diseases. In each phase of the development process, stringent rules apply to guarantee the quality, efficacy and safety of the drug ('Good Laboratory, Manufacturing and Clinical Practices'). Market authorization is only obtained upon full compliance to such regulations, which can vary from country to country. In an attempt to establish global standards with respect to the safety, efficacy and quality of pharmaceuticals, the major drug manufacturing countries (US, European Union and Japan) agreed upon a common set of guidelines through the International Conference on Harmonization (ICH) of regulatory requirements (Official website of ICH: http://www.ifpma.org/ich1.html). This initiative is a joint undertaking between industry and regulators. The quality, efficacy and safety requirements that constitute the ICH guidelines deal specifically with drug development in an affluent market, where cost is not a major issue and where safety is the prime concern. For neglected diseases, cost is a major issue and the risk-to-benefit ratio in terms of quality, efficacy and safety should be put into the perspective of the gross public health failure of having no treatment at all. However, the ICH recommendations are being regarded as absolute requirements rather than guidelines (which they are) (Trouiller *et al.* 2001). Insistence on compliance with such demanding regulations further increases the development costs and creates a major disincentive to small companies from developing countries or emerging markets trying to enter the market. In fact, only the large and wealthy companies can comply with such increasingly demanding regulations. But these are the companies least interested in neglected diseases (Wehrli 1997).

Protection of intellectual property

Inventions, such as a new drug or its manufacturing process, can be protected through patenting. A patent gives the owner the right to restrain others from producing and selling the patented product for a given period (usually 20 years) in any country where the patent has been granted. The rationale behind patent protection is to stimulate investment in R&D and to promote widespread dissemination of new and useful technologies, by ensuring return on investment via temporary market exclusivity. Northern multinational pharmaceutical companies view this market monopoly and its consequence, the setting of the sales price, as a *conditio sine qua non* to invest in drug development.

Until recently, the legal basis for patent protection of products and processes was restricted mainly to the industrialized world. For this reason, investment in tropical disease research was considered uneconomical, since adequate protection of the innovation was not guaranteed in the countries that would constitute the major market. The enforcement of the TRIPS agreement (Trade Related Aspects on Intellectual Property Rights) in the framework of the World Trade Organization (WTO) should solve the issue: all WTO member states are required to grant patents on new drugs and processes for a minimum of 20 years (http://www.wto.org/wto/intellec/intellec.htm).

But it is uncertain whether stronger patent protection will promote access to new drugs in low-income countries (Velasquez & Boulet 1999). In several documented instances, patent protection has served to prevent patients from acquiring life-saving drugs because of excessive

pricing (see for example Wilson *et al.* 1999; Chirac *et al.* 2000). The ongoing trade disputes on the local (and cheaper) production of life-saving HIV-drugs in South Africa and Thailand demonstrate clearly that availability of drugs for those who need them is not a concern of the northern drug industries, which own the patents. In addition, stronger patent protection is expected to adversely affect access to new drugs in countries which have developed a domestic pharmaceutical industry based on imitative R&D. The example of the cost-saving production of praziquantel for schistosomiasis is illustrative: with a stricter patent regime, many would have been denied this essential drug for many years (Reich & Govindaraj 1998).

While the pharmaceutical industry argues in favour of a strengthening and broadening of patent protection as a stimulus for R&D, there are growing complaints from within the scientific community that patents can become a barrier to medical progress (Boyce & Coghlan 2000; Bobrow & Thomas 2001). Patents in science promote secrecy and strongly hinder free information exchange between researchers, yet this is the basis for scientific progress. The recent trend in biomedical research to massive and very broad patenting of both the basic technologies and the common resources (e.g. the genetic material) results in a limited 'freedom to operate' to develop new findings into products (Heller & Eisenberg 1998). If new product development requires multiple (and often costly) licences on existing and exceedingly broad patents from others, promising discoveries will not even be pursued. Important discoveries and the resulting potential benefits for society will be lost – discarded because their development is either dependent on too many other patents, or because the discovery cannot be patented anymore in its own right.

Essential drugs: ordinary consumer goods or a human right?

While technological advances have increased society's capacity to control infectious diseases, the position of the pharmaceutical industry in a highly competitive global marketplace has turned drugs from a public health tool into a commodity. It is overwhelmingly clear that if the decision to invest in R&D is based purely on economic terms, there is virtually no chance that drugs for neglected diseases such as trypanosomiasis and onchocerciasis will be developed. For diseases with a significant market segment in high-income countries (AIDS and possibly malaria and tuberculosis), new drugs will be developed, but they will probably remain too expensive for the millions of patients in poor countries (until patent protection expires).

Development of essential drugs clearly requires a different framework. It is the role and duty of national governments and international bodies, such as the UN and its agencies, the World Bank and the WTO, to place global health needs high on the international political agenda. But this requires political will, a strong commitment to place health considerations above economic interests, and the enforcement of rules, regulations and other mechanisms to stimulate drug development for Neglected Diseases and secure their accessibility.

Strategies to stimulate drug development and ensure access

The attempts of national or international organizations concerned with public health to promote drug development for developing countries have thus far been largely ineffectual (Pflaker & Brudon 1998). An urgent reorientation of policy is warranted. It is essential that the pharmaceutical industry contributes to the search for solutions, both at a national and international level. But industry alone cannot set the rules of the game. In the ongoing process of creating a new world order, the global economy must be structured to address the true needs of society. Four major categories of actions should be considered.

Essential medicines R&D agenda

Mobilizing existing expertise and knowledge within the international biomedical research community to address the specific needs of developing countries will require the establishment and wide dissemination of an essential medicines R&D agenda which should list and prioritize the needs, and should specify possible disease-specific factors that need to be taken into account, such as geographical distribution, existence of different market segments or the availability of candidate drugs. Clearly, this R&D agenda will need regular updating with data from epidemiological surveillance, including the emergence of resistance. At every stage of the R&D process, the ultimate goal of obtaining effective, affordable and easy-to-use drugs should guide the R&D choices.

In combination with a specific budget allocation for neglected diseases made by the traditional funding agencies (such as governments, the European Commission, WHO and foundations), public research can be redirected towards addressing the most important global health issues. Government-subsidized industrial R&D can be made dependent on a commitment to include neglected diseases in the project portfolio.

Technology transfer and capacity building/consolidation in developing countries

Solutions for tomorrow most likely lie in stimulating and supporting developing countries to build a viable R&D-based drug industry that can generate and produce the drugs they need with adequate quality in collaboration with the public sector. This will require a serious effort in capacity-building and technology transfer, along with a supportive international policy in terms of legal and regulatory issues (see below) and investments in small or medium-sized pharmaceutical firms in developing countries. A market that is unattractive to a multinational may be perfectly viable for a smaller company in a developing country. Indeed, drug development can become a potential engine for development. Capacity building and technology transfer can be promoted via bilateral and multilateral development co-operation, but priority setting must be well adapted to the specific needs and capabilities of the concerned countries. Emerging economies may be the first target of action, and solutions for the poorest countries may be grafted on successful drug production facilities in those countries. In time, charity-driven assistance programmes should be turned into sustainable partnerships (Donald 1999).

Collaborations between northern universities and universities in developing countries should be strengthened, as well as collaborations or partnerships with industry. Operational research and new studies on existing drugs can already be conducted in developing countries. This includes the identification of new indications for existing drugs, improved formulations or combinations, and the establishment of simpler treatment protocols. For example, the treatment of malaria has improved significantly in recent years as a result of clinical studies on available (old) drugs. In the long term, capacity should be built to transfer the results of basic research to the pre-clinical and clinical phase. Production capacity is already present to a limited extent, and should be expanded.

Improve legal and regulatory environment

To overcome legal and regulatory barriers towards drug development for neglected diseases, an adapted international legislative and regulatory framework could be created. It could take the form of an international 'Neglected Diseases Treaty' that is specifically designed to stimulate R&D on effective, affordable and easy-to-use drugs and vaccines for neglected diseases and also generates a framework for ensuring access. This treaty should address the imbalance between rights and obligations under the present international treaties and agreements (e.g. TRIPS, Convention of Biological Diversity, Universal Declaration of Human Rights (UDHR), etc.) and provide new legal options to make drugs for neglected diseases a global public good. The treaty could contain specific measures to stimulate industrial involvement in R&D for neglected diseases [cf. incentives such as tax credits or reductions as provided in the Orphan Drug Act to stimulate R&D on rare diseases (Haffner 1999)], but would go beyond that (Trouiller *et al*. 1999). It should also include intellectual property issues (for example conferring to these drugs the status of global public goods), possibilities for differential pricing and licensing strategies, minimal quality, efficacy and safety standards based on cost-effectiveness and a public health approach, and last but not the least access and affordability criteria. The possible financial incentives should be linked to the ultimate goal of providing effective medicines for those who need it.

Finance drug development and ensure access

Dedicated money is needed to enable the development of new drugs for neglected diseases. This will require persuasive re-prioritizing of budget allocations by all involved players. Increased financing by national governments (North and South) and international organizations (such as the UN and the World Bank) is essential, but must not be the only source of financing. Public–private partnerships that combine engagement, finance and expertise from both sectors in addressing public health priorities should be encouraged. Also, drug development and production can be promoted as a potential engine for development in itself. NGOs and private foundations must also participate in this effort, while the pharmaceutical industry should be stimulated or directed to invest in drug development that responds to global health needs. Given that governments are granting the pharmaceutical industry a monopoly on the market for medicines, governments could in return demand that a small percentage of profits go towards developing essential medicines. Foundations could be established to fund research and development activities in accordance with the priorities defined in the essential R&D agenda. They could also provide technical support, human resources and assist in the technology transfer process.

In addition to dedicated efforts to stimulate new drug development, specific measures must be taken to ensure availability and accessibility of essential drugs. For medicines that are too expensive for patients in developing countries but for which there is no market in wealthier nations, centralized purchases are recommended. Such medicines include those used to treat trypanosomiasis, leishmaniasis, meningococcal meningitis and second-line

treatments for tuberculosis. Funding should be shared by governments, international organizations and private bodies (NGOs and foundations).

When R&D is significant for diseases prevalent in both the North and South, tiered pricing of the marketed product tailored to consumer resources seems justified.

Conclusions

Firm and dedicated measures are needed to ensure the development, availability and accessibility of essential drugs to combat infectious diseases. Emphasis should be placed on the target of making these drugs to become public goods, affordable and easy to use. Solidarity between North and South, as well as between different parts of the South, will be indispensable to achieve this goal. Capacity-building and technology transfer are the key towards sustainable solutions of the problem.

The scarcity of essential medicines to control infectious diseases in developing countries demands a significant reorientation of priorities in drug development and health policy. Instead of abandoning essential drugs as trivial consumer goods in a global free market economy, essential drugs deserve a special status in accordance with their crucial role in global welfare. It is the duty of society to provide these basic health tools to as many as possible of the world's population.

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