Developing Medicines in Line with Global Public Health Needs: The Role of the World Health Organization

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"I want my leadership to be judged by the impact of our work on the health of two populations: women and the people of Africa."[1] This is how Dr. Margaret Chan, the current Director-General of the World Health Organization (WHO), described her leadership mission. The reason behind this mission is evident. Women and girls constitute 70% of the world's poor and 80% of the world's refugees. Gender violence against women aged 15–44 is responsible for more deaths and disability than cancer, malaria, traffic accidents, and war.[2] An estimated 350,000 to 500,000 women still die in childbirth every year. The negative health implications of absolute poverty are worst in Sub-Saharan Africa and South Asia.[3] Hence, Chan aims to have the biggest impact on the world's poorest people.

This article is in two parts. The first part describes briefly the complex challenges the WHO faces in pursuing its mission. The second part focuses on one particular challenge, namely, market failures in developing medicines for diseases of the poor. After outlining the problem, the role of the WHO in addressing this challenge is described as well as recent developments.

Main Challenges for WHO

Making sure that all human beings can attain the highest possible standard of health, in line with the WHO constitution,[4] is a very complex and challenging task. A large variety of factors contribute to human health: safe and adequate food, appropriate sanitation, safe drinking water, good personal hygiene, basic health knowledge, freedom from violence and harmful practices, adequate health infrastructure, access to diagnostic and medical care, including access to drugs, as well as lifestyle choices (e.g., smoking, unsafe sex).[5]

Although 6 out of 10 prime risk factors for disease, disability, and death in developed countries are lifestyle-related (tobacco, alcohol, obesity, physical inactivity, illicit drugs, and unsafe sex), the same is true of only 2 out of 10 factors in developing countries (unsafe sex, tobacco). The majority of risk factors in developing countries are poverty related (underweight, unsafe water, indoor smoke from solid fuel, zinc deficiency, iron deficiency, vitamin A deficiency).[6]

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One billion people live on less than one U.S. dollar a day, and 2.7 billion live on less than two U.S. dollars a day.[7] Of those, 850 million are chronically undernourished, more than 1.1 billion do not have access to safe drinking water, and 2.6 billion lack adequate sanitation.[8] People who suffer such massive deprivations are more likely to be susceptible to health risks and thus enter a vicious cycle of ill health, unemployment, and severe poverty. In this context, one of WHO's priorities is to improve equitable access to medicines for patients living in the developing world. WHO works to establish good governance for medicines in member states, to improve access to and transparency of the results of clinical research and published research, to strengthen ethics review capacity in developing countries, and to incentivize research and development (R&D) in the developing world through building national and regional R&D capacity.

However, in the current system the poor not only face an affordability problem when it comes to drugs, but also an availability problem.[9] Pharmaceutical innovation is focused around the market principle. Medical treatments and services are therefore not developed in line with the global burden of disease, but are instead driven by market considerations. Of the 1,556 new drugs developed between 1975 and 2004, only 21 (1.3%) targeted tropical diseases of the developing world.[10] This market failure to develop medicines for the global poor is clearly of concern to the WHO. The second part of this article therefore looks at the role of the WHO in its efforts to align medical and pharmaceutical research with global public health needs.

Market Failure to Develop Medicines for Diseases of Poverty: The WHO's Role

According to various legal instruments, state institutions bear the primary responsibility for ensuring that human beings can enjoy the highest possible standard of health. This obligation extends to providing international assistance to those states that are unable to comply without foreign aid.[11] At the same time, it is the primary duty of pharmaceutical companies to undertake research and provide medicines and health services to improve people's quality of life. Within the market system, this has to be done in a profitable manner.[12] The WHO can act as a mediator and neutral broker between states, which are responsible for respecting, protecting, and fulfilling the human right to health, and the pharmaceutical sector, which can contribute relevant products and services.

However, the WHO's role is not primarily to incentivize the pharmaceutical sector *directly* but to facilitate and complement its activities so as to achieve an alignment with global public health needs, especially those of the developing world. The WHO provides a neutral platform and acts as an independent broker and convenor on important and controversial issues. When states cannot secure human rights for their citizens because of reasons of poverty and where incentives do not exist for neglected disease research, then the WHO is needed to function as a mediator.

Two examples of how the WHO can encourage neglected disease research are promoting public–private partnerships, including product development partnerships, and convening working groups to provide expert advice to decisionmakers and resolve controversial issues.

Promoting Public–Private Partnerships

Public–private partnerships (PPPs) are collaborations between state institutions and private sector companies, usually with clearly defined goals. A good example of a PPP that operates in the area of neglected disease research is the Medicines for Malaria Venture (MMV). MMV is a not-for-profit organization, registered in Switzerland in 1999, that aims "to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating delivery of new, effective and affordable antimalarial drugs."[13] Simplified, MMV collects public and private funds, which are invested first in research undertaken at academic institutions and then in bench-to-bed efforts by pharmaceutical companies in order to bring developments to market. A malaria drug based on research by the MMV is currently under approval by the European Medicines Agency. If approved, it would provide a drug with an estimated 95% efficacy and a simple dosing regimen, which would be an important tool in the fight against resistance to a disease that exists almost exclusively in developing countries.[14]

A subclass of PPPs are product development partnerships (PDPs), which focus specifically on drug or tool development for neglected diseases. A good example of a PDP is the Foundation for Innovative New Diagnostics (FIND).[15] This Geneva-based foundation with offices in Uganda and India focuses its work on the development of technologies that help in the diagnosis of infectious diseases. It is funded and supported by around 150 organizations, companies, and institutions, including the WHO. One of the diseases on which FIND concentrates is human African trypanosomiasis, or sleeping sickness. Sleeping sickness is a vector-borne parasitic disease, transmitted by tsetse flies. Rural populations in remote areas are particularly prone to infection, and healthcare systems in such areas are often weak or even nonexistent, so the development of diagnostic tools that can be used "as near as possible to where patients first seek care"[16] is particularly important.

PPPs and PDPs are a good example of how the WHO's convenor role can function by bringing together those with the primary responsibility to deliver on the human right to health (state institutions) with those with the capacity to provide the relevant means (academic and pharmaceutical research as well as implementation NGOs). The WHO promotes PPPs and PDPs by giving initial recognition and support in terms of reiterating the importance of the initiative and occasionally by hosting the initial meetings and discussions. The WHO also provides technical advice through specific programs in the relevant areas. This in-kind support and the association with the WHO give more visibility to such initiatives.

Working Groups

The WHO regularly convenes expert working groups to provide information on pressing topics and to resolve critical issues. One such issue is the provision of healthcare products to poor populations, both in terms of product affordability as well as product availability (neglected disease research). In May 2006, the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG) was established by the Executive Board of the WHO. Its mandate was "to prepare a global strategy and plan of action on public health,

innovation and intellectual property to address conditions disproportionately affecting developing countries.''[17]

Over the next two years, the IGWG organized three stakeholder meetings together with WHO member states, in addition to inviting written submissions and conducting two Web-based public hearings. The *Global Strategy and Plan of Action* (GSPA) delivered by the IGWG to the World Health Assembly in May 2008 was adopted with resolution WHA61.21.[18]

The GSPA has eight core elements:[19]

1) prioritizing research and development needs
2) promoting research and development
3) building and improving innovative capacity
4) transfer of technology
5) application and management of intellectual property to contribute to innovation and promote public health
6) improving delivery and access
7) promoting sustainable financing mechanisms
8) establishing and monitoring reporting systems.

In terms of providing incentives for neglected disease research, point 7 (promoting sustainable financing mechanisms) is the most relevant. As part of WHA61.21, the World Health Assembly requested of the Director General Dr. Margaret Chan:

> 4(7) to establish urgently a results-oriented and time-limited expert working group to examine current financing and coordination of research and development, as well as proposals for new and innovative sources of funding to stimulate research and development related to Type II and Type III diseases and the specific research and development needs of developing countries in relation to Type I diseases.[20]

An Expert Working Group on Research and Development Financing (EWG) was created in May 2008. In December 2009 it delivered its report *Research and Development Co-ordination and Financing* to the Director General, recommending that the WHO take certain actions and linking these actions to the implementation of the GSPA.[21] The report noted that there is still no indication that Type II and Type III diseases are adequately researched or that relevant healthcare products are being developed. It also noted that intellectual property rights do not provide the commercial incentives needed to improve public health in developing countries. When the market fails to secure a public good, such as drugs tailored to the diseases of the poor, public funds need to be generated and used, according to the EWG. Three suites of efforts were included in the EWG's recommendations in order to supplement the intellectual property rights system: financing proposals, funding allocation proposals, and efficiency proposals.

Financing proposals. To generate the income necessary to fund pharmaceutical research and development on neglected diseases from public sources, three methods were recommended:

- Indirect consumer taxes. Possible examples of an indirect consumer tax would be a tax on the arms trade market, a digital tax charging for Internet

traffic, or a financial transaction tax, which imposes a tax on banking transactions.
- Voluntary and individual business contributions. This approach favors donations as the main fundraising mechanism, possibly linked to certain transactions (e.g., bill payment). As an example, the group estimated that the airline voluntary solidarity contribution scheme raises around US$1 billion per annum.
- New donor funds for health research and development. Donations from new, nontraditional donors were also regarded as a possibility by the EWG, in particular, donations from countries that are not currently included in the Organisation for Economic Co-operation and Development Development Assistance Committee, such as China, India, and Venezuela.

Funding allocation approaches. Raising funds alone is, however, not sufficient to achieve a goal; the optimal allocation of funding needs to be assured in order to achieve maximum impact. The EWG therefore recommended five different mechanisms that could be used by multiple bodies and organizations in order to have the optimal effect on public health in developing countries:

- Funding via product development partnerships. As noted above in the first section, PDPs are a form of public–private partnership.
- Direct grants to small and medium-sized enterprises and grants for developing country trials. Direct project grants for small developers, for instance, small diagnostic firms, were rated as one of the best approaches to stimulate research into neglected diseases by companies themselves.
- Milestone prizes. Milestone prizes are cash rewards for moving on a particular development pathway toward, for instance, a vaccine for a given disease. Although the prizes are paid before the end result is achieved, this provides incentives to undertake basic research. One prize system that was recommended by the group was InnoCentive. Founded in 2001, this initiative brings together those who want to solve a particular problem (i.e., those who require an innovation) with those who have the skills and knowledge to solve it. As expressed in their mission, InnoCentive "believe in the power of open innovation, bringing together creative minds to create breakthrough solutions that touch every human life."[22] According to the EWG, "InnoCentive-style milestone prizes are a highly cost-effective way to encourage small firms to generate innovative solutions to basic research questions and technical problems up to the point of clinical development."[23]
- End prizes. In contrast to milestone prizes, end prizes give a large cash sum once a particular product, for instance, a vaccine, has been developed in full. Such end prizes could, for instance, be regarded as paying the developer for the intellectual property rights.
- Purchase or procurement agreements. To reduce the innovation risk for developers, purchase agreements can make sure that there is a market for the product under development. A prior contract will establish that the product will be bought at a certain price and at a certain volume.

Efficiency proposals. After funds have been raised and allocated optimally to pay for research and development, it is still possible to achieve a higher output

through prior agreement of efficiency reforms. Two such reform plans were suggested by the EWG:

- Regulatory harmonization in developing countries. Research and development is only part of the cost of pharmaceutical innovation. Bringing a product to market is another part. Currently, regulatory requirements to obtain market approval are different between countries and regional alliances. If these regulations were harmonized, more funds could be devoted to research and development rather than complying with diverse ways of making sure that a product is safe, effective, and of high quality.
- Precompetitive R&D platforms. The development and distribution of research platforms prior to intellectual property rights protection should be encouraged. Essentially, such platforms work on a collaborative principle, even when competing firms are involved. Firms agree to pool competencies and resources in order to overcome problems that are holding them back collectively. Such research platforms might, for instance, involve the exchange of animal models or genomic sequence databases.

Finally, the group recommended that ''efforts should be made to examine other promising proposals in their local contexts, such as open source products; patent pools; Health Impact Fund; priority review voucher scheme; and orphan drug legislation.''[24]

Open source products usually involve voluntary contributions from a variety of skilled people (e.g., computer programmers) who work on a common product prior to making it available to other users for free. Patent pools are reciprocal agreements between patent holders to forgo a license fee in the event the other party uses the patented tool or product in new developments.

The Health Impact Fund (HIF) is a mechanism proposed to supplement the intellectual property system by offering pharmaceutical innovators a 10-year reward based on the impact their product has on the global disease burden. The HIF has been described in more detail in earlier volumes of this publication.[25]

Priority Review Vouchers give an innovator the right to demand expedited review for a particular drug when registering a drug for a neglected or tropical disease. In other words, if one invents a new drug for river blindness one can thereby speed up the approval time for a blockbuster drug. Orphan drug legislation provides incentives such as tax cuts or enhanced patent protection to those who develop medicines and services for neglected diseases.

These proposals were the subject of extensive debate and discussion at the WHO Executive Board in January 2010 and again at the World Health Assembly in May 2010. Another IGWG is likely to be convened to consider this further.

Conclusion

The World Health Organization's main priority is to improve equitable access to medicines for people and patients living in the developing world. In this regard, it has acted as a neutral broker to provide a platform for discussing important issues such as the need to link innovation with access, to delink R&D costs from pricing of medicines, and to explore feasible and workable alternatives to the traditional IP regime as an incentive mechanism. In a complex landscape with

many actors and a diversity of options, the WHO needs to work more closely in the future with other international organizations (e.g., World Intellectual Property Organization and World Trade Organization) and important stakeholders, including the pharmaceutical industry and PPPs/PDPs. For the sake of sustainability, these efforts need to be pursued in parallel with the building and strengthening of R&D capacity and self-sufficiency in the developing world.

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