New models for pharmaceutical innovation in low-income countries

Given today's pharmaceutical markets, it is difficult to develop new drugs for diseases that primarily affect people in developing countries. Supplementary business models are needed to address this. Experience with developing drugs for rare diseases gives some insight into promising incentive structures, but we also need new mechanisms such as prizes, open source, research funds and product development partnerships. Norway should support mechanisms of this kind, both at home and abroad.

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New drugs are primarily developed where markets function and innovators are rewarded for their efforts. The incentive is a patent, a temporary monopoly where the owner can set the highest price that the market is willing to bear. This model functions for medicines related to such illnesses as asthma, cardiovascular disease and diabetes, diseases that are common in prosperous countries like Norway. Investment in research and development (R&D) becomes profitable when there are a sufficient number of insured or wealthy patients. When the market does not function because of insufficient demand and/or inability to pay, a gap develops between innovation and needs. As a result, the R&D necessary for the development of new medicines does not take place. This market failure occurs when markets are too small (e.g. rare diseases) or too poor (e.g. neglected diseases that are found primarily in developing countries). New, innovative business models have been established or proposed to close these gaps. Some potential models directed at neglected diseases are described below, but first an account is given of what has been achieved with respect to rare diseases in wealthy countries.

Rare diseases

The existing patent model has been strengthened by providing further economic incentives to promote rare disease R&D. Legislation regulating orphan drug development has been introduced in the USA (1983) and in Europe (1999) to stimulate research and development of drugs for rare diseases with a mixture of economic push and pull mechanisms. Push mechanisms reduce the R&D cost or risk for all types of drug development (e.g. research grants). Pull mechanisms reward the results (e.g. prizes for the research result that created the best solution) (1) (Table 1).

Orphan drug legislation contains economic incentives such as tax deductions, regulatory fee exemptions, priority regulatory review and extended market exclusivity periods. This is in addition to the patents themselves. The result is that hundreds of new drugs have been developed, so market failure appears to have been compensated for.

However, drugs for rare diseases in most cases have very high prices. They are so high that despite the limited market, some have achieved sales of more than USD 1 billion annually (2). Pharmaceutical companies have reaped the benefits of both the patent model and additional regulatory incentives. The USA's Orphan Drug Act, but not the EU version, includes neglected diseases, since these affect few Americans and are therefore regarded as rare. However, the needs of an American who contracts malaria on holiday and a Ghanaian who is exposed to infection during much of the year are very different. Long-term use of a medicine places greater demands on safety. The Act has therefore had little effect on the development of new drugs for diseases that affect people in developing countries. Other solutions must be found for neglected diseases.

Drugs for neglected diseases

In 2006, member states of the World Health Organization (WHO) established an intergovernmental working group on Public Health, Innovation and Intellectual Property. Its mandate is to look at diseases that disproportionately affect developing countries with a view to creating medicines. A Consultative Expert Working Group (CEWG), established in 2011, is considering new and innovative models for stimulating the funding of R&D directed at the needs of developing countries for medicines and related products, such as diagnostic tools.

The basic concept of these new business models is to de-link the cost of research and development from the price of the final product. The estimated cost of developing a medicine is contested and varies from EUR 100 million to EUR 1 billion (1, 3). If medicines are to be made accessible to patients in developing countries, the final prices cannot be set on the basis of total cost, no matter what the development cost might be. That would make prices too high. R&D costs and prices must be regarded as two separate and independent calculations.

The Consultative Expert Working Group will evaluate these business models that aim to de-link price from cost. Almost 100 different models have been proposed, most of them untested (4). In order to exemplify the models, we will discuss three different types of proposals: prizes, an R&D fund and open source drug discovery, as these provide a good picture of the whole range of models.

Prizes

Prizes are a pull incentive that is often promoted as an ideal method of achieving de-linking. The idea behind a prize is to post a large enough reward to encourage a number of innovators to conduct research according to given criteria for what the final result is intended to achieve. The first innovator to satisfy the criteria is awarded the prize. Funding institutions generally like prizes since they generate a lot of activity while only paying for success. The risk to the funder is low, whereas the risk to the innovator is high. This high risk means that only product developers that can sustain the risk and secure financing for the research can take part in the competition. This may exclude valuable contributors. Milestone

prizes have been proposed to mitigate this disadvantage. Instead of awarding a prize only for the final product, milestone prizes allow awards for incremental innovation.

The American non-profit organization Results for Development Institute (R4D) has evaluated prizes in a drug development context (5) and found that prizes may incentivize R&D investment as long as the prize is large enough and the contest well designed. R4D's analyses indicate that the prize model is most useful if two conditions are met: first, there must be a need for new ideas to overcome scientific or technological barriers; second, innovators must themselves be able to find supplementary financing to subsidize their work. An R&D fund may be a supplementary source of financing.

Research and development funds

Global R&D funds have been proposed to support research and development needs in low-income countries. The idea is that the fund should be coordinated globally and cover all stages of drug development, including expensive clinical trials, transfer of technology and capacity-building. A fund could finance some of the other proposed models, such as prizes and grants, depending upon the challenge and the disease. Bangladesh, Barbados, Bolivia and Surinam have proposed such a fund as a treaty commitment for WHO member states (6), i.e. if there is consensus, all member countries would be obligated to finance the fund. At present most development is financed by national development agencies, like NORAD, or private funds such as the Bill & Melinda Gates Foundation. The proposed fund appears to be a more coordinated approach.

Open source drug discovery

The term 'open source' is derived from the management of a product's intellectual property rights. An open source product is one where the design is freely available for anyone to use, modify and distribute. This push model is attractive because it may require less financial support than other models. The concept of open source is a complex one, but when it comes to adapting it to drug development, two specific aspects are desirable: collaboration between researchers, often without remuneration, and the open approach to intellectual property rights.

This model originates in the software industry where unpaid collaboration mainly takes place because there are other incentives than remuneration, for example learning, signalling of expertise and the sale of complementary products. Most of these incentives will in principle also apply in other industries and sectors, but the advantage of software is that it is not consumable – individuals can copy the product without lowering the value of the original. More-

| Table 1 Pu | ush and pu | Ill mechanisms fo | or stimulating | research and | development of | new medicines |
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| Push mechanisms | Pull mechanisms | | |
|---|--|--|--|
| Research and development grants | Extended market exclusivity | | |
| Accelerated regulatory review | Government-guaranteed future procurement | | |
| Open source drug discovery | Purchase funds | | |
| Tax deductions for research and development | Patents | | |
| Open access to publicly financed research | Prizes | | |
| | Tax deductions on sales income | | |

over, development costs, aside from programmer time, are low.

Several open source drug discovery projects exist today. Two of the biggest are CSIR Team India's Open Source Drug Discovery and the Synaptic Leap. However, many questions remain unanswered about the model, e.g. how can it be applied to patents rather than copyright (used in the software industry) and how are the costs of laboratories and physical goods to be covered? The two projects mentioned above have both secured external financing.

New comprehensive development models

These new models should not be assessed separately or viewed independently of one another. It will probably be more practical to regard them as parts of a new, comprehensive research and development system (Fig. 1). Open source is most appropriate for the early stages of the development process of new drugs, where some of the work is theoretical and can be done virtually. When a promising substance (lead compound) is identified, the problems associated with optimization and further development can be resolved by means of milestone prizes. Finally, the expensive clinical trials can be paid for through grants from a research and development fund. Drug development is a highly complex process that requires new and inventive thinking to lead new, promising candidates through the

product development life cycle. Leadership and control are necessary if one is to end up with an efficacious drug. This is where product development partnerships come in.

Product development partnerships are often non-profit enterprises whose aim is to develop new drugs for neglected diseases. They are largely financed by public or philanthropic sources. Examples of established product development partnerships are Drugs for Neglected Diseases Initiative (DNDi) and International AIDS Vaccine Initiative. Product development partnerships often employ people from the industry who have considerable experience in developing drugs. They use hybrid business models based on a selection of push and pull mechanisms suited to the development phase. They commission both private and public organizations to carry out tasks, often in developing countries, in order to keep costs low and promote capacitybuilding. Drugs developed by product development partnerships are not necessarily patented. Many will circumvent patents and make knowledge freely available (for example DNDi). This means that developing countries can use the knowledge without paying or notifying the innovator. Product development partnerships have created a great deal of research and development activity for neglected diseases, with almost 150 new candidates in the pipeline including drugs, diagnostic tests and vector control mechanisms (1).



Figure 1 Interaction between proposed research and development incentives in connection with the development of new drugs for neglected diseases.

Most of these models depend on public or philanthropic support since they do not have an income-generating function. Their sustainability is therefore open to question, particularly in difficult economic times. WHO has recognized this problem and has instructed its working group to identify new funding mechanisms. One example under consideration is micro transaction taxes, such as taxes on financial transactions or airline tickets. Another is a solidarity tax on tobacco products. Fifteen countries have introduced a micro tax on airline tickets and have managed to raise more than USD 2 billion for UNITAID (an organization launched by the UN General Assembly in 2006 for the purpose of improving developing countries' access to medicines). Norway has decided not to introduce tax on airline tickets; instead CO2, emissions from aircraft fuel are taxed (7).

Norway's role

Norway is a substantial financial contributor to neglected disease R&D, contributing more than USD 17 million in 2009 (8). Norway supports product development partnerships, purchase funds, regulatory harmonization in developing countries, open source drug discovery and is a partner in UNITAID. John-Arne Røttingen, former director of the Knowledge Centre, also chairs WHO's working group (CEWG). This demonstrates that Norway is taking initiatives in the struggle against neglected diseases. However, little R&D on these diseases takes place in Norway.

The global health research that is carried out in Norway is presented in the report Global helseforskning [Global health research] (9), published by the Norwegian Directorate of Public Health in June 2008. When it comes to tropical diseases, the report only has two small research communities to refer to: Ullevål University Hospital and the University of Oslo, performing research on schistosomiasis, and the National Centre for Tropical Infectious Diseases at Haukeland University Hospital, which is researching tuberculosis, the parasite Giardia lamblia and antimicrobial resistance in Tanzania. Since these are diseases that do not affect us in Norway on the whole, it is not really surprising that this research is so limited. A Norwegian doctor can therefore go through an entire professional life without encountering these diseases.

Is it wrong for there to be limited

research on tropical diseases here in Norway? No, not necessarily. But as a wealthy country, Norway has a responsibility - with respect to both financial resources and research expertise. Norway's support through NORAD of research in developing countries is positive, but we ought also to build our own communities to contribute to the international work. Developing countries need capacitybuilding in order to help them to help themselves as well as money for research. Norway does this by contributing funding, for example for product development partnerships. In this way, Norwegian researchers can also contribute if they have unique, necessary expertise, preferably through north-south cooperation, where Norway cooperates with institutions in the south. North-south cooperation can facilitate access to equipment, capital and other resources, and can assist in developing sustainable research environments in developing countries. This is also in line with Norway's development assistance policy on institutional cooperation.

Product development partnerships have already had some success in placing R&D focus on neglected diseases. If this focus continues with new business models and increased assistance, neglected diseases may perhaps attract more interest and funding.

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