Aligning pharmaceutical innovation with medical need

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How can we make vaccines and medicines for major diseases that have been largely ignored? How can we get vaccines and medicines to populations that cannot afford them? A fundamental solution to these problems requires aligning three basic processes—innovation, incentive and access—so that they become mutually reinforcing. The present patent system provides incentives for innovation by enforcing product monopolies that permit sales at prices far above production cost. Industry has little financial incentive to develop products for diseases that mainly afflict the poor, and the poor cannot afford products that industry develops for wealthier customers. Two reforms could correct these disparities and benefit all stakeholders. First, open-access drug companies—fee-for-service sites within drug companies for collaborations among academics and biotechnology and pharmaceutical professionals, funded by users and government—would bring new ideas and expertise to the development of drugs independent of market drivers. Second, a patent track that rewards innovation in proportion to its impact on the global burden of disease would provide an incentive for pricing near the cost of production and commit government and business to improving health care delivery. Allying open access and traditional drug companies and offering a credit-assignment patent track alongside the monopoly-enforcement track would increase the number and accessibility of medical interventions, industry's therapeutic and geographic opportunities, and global health.

We must reform how we make and distribute vaccines and drugs. This call is coming from diverse quarters: business school professors, economists, jurists and pharmaceutical executives. They write: "The global system of drug development and marketing is broken..."[1]; "The system is ill-adapted to develop products of great social need..."[2]; "In developing countries, life-saving medicines are priced beyond the reach of most people, a morally offensive outcome"[3]; the "flow of new drugs has slowed to a trickle..."[4]. Something is wrong when President Clinton had to devote much of his energies to negotiating price reductions so AIDS drugs could reach just a few of the children who need them[5].

The issues come into focus if we discuss them with reference to three categories of diseases[6] and three economic concepts. Type I diseases, such as cancer, afflict people everywhere, not only in economically developed countries but also in less developed countries. Type II diseases, such as tuberculosis, strike everywhere but are far more prevalent in less developed countries. Type III diseases, such as filariasis, are encountered almost exclusively in less developed countries. The three economic concepts as used here are 'innovation', drug and vaccine research and development and the manufacture of resulting products; 'incentive', financial returns adequate to sustain production and new research and development (R&D) while attracting investment; and 'access', the impact of price and health care infrastructure on the ability of populations to use medical products.

The current system for commercial drug development (**Fig. 1a**) provides incentives for innovation for treatments of type I diseases by providing rewards through patent-based monopoly pricing. This system offers inadequate monetary incentive for commercial innovation for diseases of types II and III. Médecins Sans Frontières (MSF) brought this forcefully to the fore in 1999: "Among the 1223 new chemical entities commercialized from 1975 to 1997, ... only 13 (1%) are specifically for tropical diseases... and only 4 (0.3%) may be considered direct results of R&D of the pharmaceutical industry..."[7]. Much clamor and a Nobel Peace Prize for MSF notwithstanding, the number of new medicines for diseases of types II and III remains proportionately miniscule today[8]. However, the present incentive system also adversely affects people with type I diseases, including people in developed countries. For example, despite rapidly spreading drug resistance[9–11], there is insufficient R&D for antibiotics, in part because monopoly-based drug development and the perception of relatively small markets converge to discourage development of treatments specific for precisely diagnosed conditions using combinations of individually owned agents[12,13]. Finally, since the vast majority of the people in the world are poor, a system in which profits are derived from sales makes most drugs inaccessible to most people[14–17]. The cost of society's failure to prevent and treat disease is staggering, not just to individuals, families, communities and governments, but also to business. Ill health is a major driver of poverty, and poverty deprives business of workers and markets.

Figure 1b illustrates the benefits of aligning innovation, incentive and access and provides a framework for evaluating numerous recent proposals, many of them now under consideration by the World Health Organization Intergovernmental Working Group on Public Health, Innovation and Intellectual Property Rights[6] (**Table 1**). We should vet these proposals with two questions. First, which are feasible? Feasibility does not mean that which requires the least in leadership, work, change or cost. Feasibility means improving the lot of all the major stakeholders (patients, governments, and makers of health care products) with net costs to governments and philanthropies that are not much larger than the sums

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they already spend for medical R&D and the purchase of vaccines and drugs. Second, given that no one change could make innovation, incentive and access mutually reinforcing, what is the minimum combination of feasible changes that could do so?

Two changes meet these tests: (i) the establishment of open access drug companies alongside and within traditional companies[9] and (ii) a patent track that provides financial reward in proportion to medical benefit[2,15,18,19], alongside the traditional system, in which rewards derive from sales.

Open-access drug companies

The last few years have brought good news for R&D for diseases of types II and III: the advent of public-private partnerships (PPPs)[20]. Some 24 PPPs managing ~$900 million from philanthropy and ~$244 million from governments have identified targets or lead compounds, chiefly in academia, for which the owners of the intellectual property consent to not-for-profit distribution in less developed countries[6]. The PPPs contract with biotechnology and pharmaceutical companies to carry out various aspects of development; this has resulted in over 47 potential products for type III diseases[6].

Most drug companies lack expertise in the biology of type II and III diseases. The success of PPPs shows that it is possible to connect those who have biological expertise with those who have pharmaceutical tools. However, philanthropy lacks the means to carry this load indefinitely. Each infusion of philanthropic funds into PPPs has had a short time window, impacting the type of project that PPPs can support. PPPs cover only a few diseases. They have the resources to pursue a small fraction of routes of interest. Given the constraints on time and resources, PPPs are forced to take a layer-cake approach to drug development: academics carry out early research, usually without benefit of access to appropriate compound collections, screening facilities, medicinal chemists or pharmacologists; then medicinal chemists, pharmacologists and others take over to try to improve the unnecessarily small number of what are likely to be suboptimal lead compounds. In contrast, optimal drug development requires that pharmaceutical professionals participate with biologists from the outset, helping to choose compound libraries, evaluate hits from both chemical and pharmacologic viewpoints and select and modify early lead compounds[21]. In short, there is great benefit of frequent contact among team members with the diversity of expertise generally found only in large pharmaceutical companies[1].

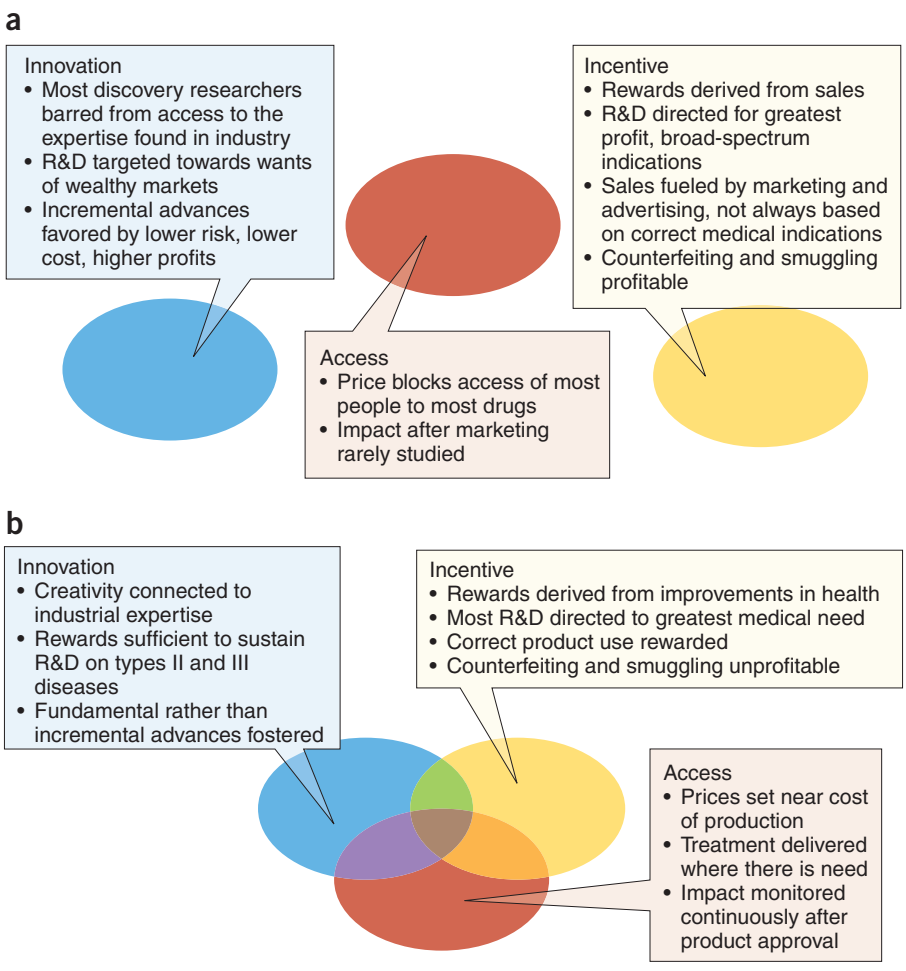

Figure 1 Alternative relationships among innovation, incentive and access. (**a**) Problems of nonalignment. (**b**) Goals of alignment.

Open-access drug companies funded by users and government could institutionalize and improve the best features of PPPs. Open-access drug companies are envisioned as contract-based frameworks and sites for collaborations between academics and drug companies and among companies. Pharmaceutical companies would be enlisted as hosts in several geographic regions. For a base fee, a company would designate a sector of an R&D facility in which it would permit approved scientists from academia and other companies. Admission of users and allocation of funds for specific projects would be controlled by a site management board, appointed by and employed by the funders and including pharmaceutical professionals. The management board would prioritize projects that offer hope of meeting substantial medical needs that are not otherwise likely to be addressed. Leading examples are narrow-spectrum antibiotics for type I infections; preventive and therapeutic approaches to diseases of types II and III; therapies designed to be used in combination (for example, to treat infectious diseases and cancer); and cancer chemoprevention. Scientists would apply to the management board for access, on a fee-for-service basis, to medicinal chemistry, molecular modeling, pharmacology (including pharmacokinetics and pharmacodynamics), formulation and toxicology. The earlier the phase of the work, the greater the share the scientist would have to cover from his or her grants or with support from his or her employer. As an academic project became more costly, it would compete with others for peer-reviewed government funding. Collectively the management boards would identify redundancies and potential synergies among projects.

Intellectual property would be assigned to inventors as defined by patent law. Employees of the host pharmaceutical company would share inventorship as their contributions warranted. However, the open-access contract would require that control over the use of intellectual property would be vested with the funders, not the contractees. The funders

Table 1 Suggestions for improving the impact of pharmaceutical research, development and utilization on global medical need

Suggestion	Advantages	Shortcomings
Companies donate drugs	Drugs are free; good publicity for donors; suited to time-limited disease eradication programs	a,b,c,d
Companies donate IP rights	Drugs can be priced near cost of production; good publicity for donors	a,b,c
Universities donate IP rights to not-for-profit drug developers (e.g., OneWorld Health)	Drugs can be priced near cost of production; good publicity for donors	a,b,c
Companies set up R&D units dedicated to type II and III diseases: e.g., GlaxoSmithKline in Tres Cantos, Spain; AstraZeneca in Bangalore, India; Novartis Institute for Tropical Diseases in Singapore; or devote resources internally (Johnson & Johnson, Otsuka, Bayer)	Innovation anticipated; good publicity for companies	a,c,e
Government doubles support for biomedical research, devotes the increment to drug R&D at publically funded research corporations with patents placed in the public domain: Free Market Drug Act of 2004[16]	Might lead to more drugs at lower prices	a,f
Governments pay for a larger portion of drug R&D in government, academia or drug companies; recipients forego monopoly; costs met from mandated contributions by individuals or employers[3] or by governments by treaty[30,31]	More public funding for R&D; governmental rather than private choice of targets; lower prices	a,b,g
Universities conduct R&D for type II, III diseases with help from government and philanthropy to include medicinal chemists[20,32]	Examples exist; provides academics with facilities like those at small biotech companies	a,c,e,g
PPPs (philanthropically funded) use contracts to manage drug development at diverse sites in biotech or pharma	Professionally managed without profit drivers; efficient distribution of tasks among contractors near cost	a,c,g
Tax incentives favor R&D for high medical need and can be invested or traded[33]	Encourages innovation	b,e
Extend Orphan Drug Act to cover type III diseases (fast-track approval, 7-year extended market exclusivity, 50% tax credit on clinical trials)[34]	Has led to many new drugs in what would otherwise be financially unrewarding markets	b,e,k
Wild-card patent extension for producing drugs for type II and III diseases	Encourages innovation	d,e,f,l
Advance purchase commitments[35]	May lead to new products	a,d,i,j,m
Tiered pricing[36,37]	Improves affordability to some users; already in widespread use with relatively narrow differentials	b,c,f,h,i
Price controls	Improves affordability	b,c,d,i,j
International pooled purchasing consortia	Negotiates lower prices	a,b,c
Compulsory licensing to permit patent violation by a producer who sells at lower cost	Improves affordability to some users	b,c,d,h
Obligatory choice of protecting patents in either rich or poor countries, not both[14]	Lowers cost of drugs for type I diseases in less developed countries; encourages in-country production	b,c,e,h
Buyout or prize system (government provides patent holder its profit)[38]	Improves affordability	a,d,i,j
Patent buyouts by auction[39]	Allows lower pricing	a,d,i,j
Conduct R&D in new sites funded by government, universities, NGOs and pharma, with distribution at cost in poor areas and for profit in wealthy areas[9] (see text for revised approach)	Allows R&D for all diseases or approaches lacking market drivers	c
Reward global disease burden reduction from a government fund, for example, by 'track II' patent registration (see text)[2,3,15,18,19,28]	Encourages R&D for high medical need; governments and insurers have experience with DALYs in including drugs in formularies[15]; fall in drug prices would save money for government, business	initially c, j

Abbreviations and special uses of terms: DALY, disability-adjusted life year, the equivalent of a lost year of healthy life; drug, all products useful for health, including vaccines; incentive, funds to pay for research and development plus profit; IP, intellectual property; NGO, nongovernmental organization; R&D: research and development; university, any not-for-profit institution dedicated to research and education.

[a]Limited coverage by disease, or limited involvement of useful participants (for example, scientists or companies)
[b]No incentive, no incentive to address needs of less developed countries, or no incentive to address type II and III diseases
[c]Not economically self-sustaining
[d]No incentive to market, distribute, and/or make subsequent improvements in products
[e]Does not address problems of access
[f]Politically objectionable
[g]Insufficient experience in or failure to include one or another critical stage of drug development
[h]Backflow of drugs from low-price to high-price regions, or movement of patients from developed to less developed countries for treatment
[i]Governments heavily influence which drugs will be most widely used
[j]Difficult to assign fair value
[k]Has led to extraordinarily high prices; has not attracted most large firms
[l]Only attracts firms holding lucrative patents; increases costs for other drugs
[m]Does not improve access to existing drugs; uncertainty in ability to meet specifications and winner-takes-all reward are disincentives; race to the finish discourages risk-taking science, without which there may be no effective product

would register patents under track II, described below. Profit would be shared among owners of intellectual property in accord with a predetermined policy that included procedures for resolving disputes without litigation.

Some users of the open-access drug companies might have completed chemical screens elsewhere; some might be able to screen the host company's chemical compound collections as a collaboration. However, a major goal of the open-access drug companies would be the collection, expansion and curation of new, open-access chemical libraries of particular promise for infectious disease. These libraries would feature natural products from underexplored sources[22], such as marine actinomycetes[23], plants[24] and uncultured organisms from which operons are cloned for expression in recombinant bacteria[22]. The libraries would also include privately held compounds donated to promote discovery of new uses, such as drug candidates whose development had been halted and the archived precursors or analogs of existing drugs[25]. Compounds that had already been patented could be donated to the collection if licensed for potential new uses by way of patent track II (discussed below); the license could assign donors a share of profits. Given the urgency of creating[26] and sharing[27] new compound collections for antibiotic R&D, access to the compound collections would be provided not only to academics but also to companies. Users would pay a fee to defray costs and return to the open-access system a proportion of resulting profits. Those using the libraries could patent their own derivatives of the compounds in the screening collection, but not the open-source compounds themselves.

Some aspects of these ideas are now being tried. For example, Pfizer is sharing 12,000 compounds with scientists affiliated with the WHO's Special Program for Research and Training in Tropical Diseases (TDR), and allowing TDR scientists to work at a Pfizer site with company scientists to develop lead compounds[20]. At least 13 other companies are providing compounds to TDR and several are offering medicinal chemistry and pharmacokinetic services[20].

Track II patents: a new system of rewards

The second crucial adjustment required in the relationship of the pharmaceutical industry to society is a patent track that directly aligns incentives with medical need[3,15,18,19,28]. This proposal refers not to how a patent is sought or awarded, but to how it is applied—either to enforce a monopoly (the present track, here called track I) or to earn credit for utility, which Thomas Pogge calls 'track II'[19]. Below is described one vision of a reward system based on assignment of credit. Choosing track II would be voluntary, and a company would be able to switch a given product from track I to track II as it recalculates its prospects for profit. Under track II, governments of developed and developing countries would make multiyear commitments to contribute to a large fund (eventually on the order of tens of billions per year, expressed in US dollars) from which owners of a registered patent could opt to be paid periodically in proportion to the product's contribution to reducing the global burden of disease. Contribution would most probably be assessed by projected and actual impact on quality-adjusted life years. Assuming continued product use and benefit, payments could continue longer than the life of the patent: for example, up to 20 years from patent approval. In contrast, track I only protects monopoly for 20 years from patent filing; the prospect of an extended reward period could help attract innovators to track II. Unlike advance purchase commitments, track II would encourage continued product improvement to compete for ongoing payments.

Track II would reward patent owners who address the most serious and widespread diseases and get their products to the largest possible number of people. Access would be increased by lowering the product's price to near (or even below) the cost of production and by granting royalty-free licenses to (or even hiring) in-country firms for manufacture. The attraction for counterfeiters who sell imitation drugs would drop with the price. Governments contributing to or benefiting from the fund and pharmaceutical firms competing for payments would all gain advantage from promoting health care infrastructure, teaching providers and consumers how to use products and ascertaining the impact.

For products registered on track II, government would have no need to impose price controls, negotiate discounts or legislate against importation of lower-price products. Instead, government would play a completely different role: to accelerate its effort to reward health care interventions on the basis of performance[29] by investing in improved health care statistics, projections and monitoring. As the number of people afflicted by type I diseases is greater in developing than in developed countries[40], companies may profit by shifting some products for type I diseases to the track II reward system. As that shift occurs, the cost to developed-country governments of the reward fund and the bureaucracy that allocates rewards would be correspondingly offset by the marked reduction in the price of drugs for which government pays[15]. Governments would collect increased tax revenues in developed countries as profits rose in the business sector from decreased spending on employees' drugs, and in developing countries as a healthier workforce increased productivity. Drug companies would benefit as additional diseases became rewarding to treat and new populations became medical consumers.

Conclusions

Using substantially the same funds they now spend on research, development and delivery of health care products, governments and philanthropies could restructure working relationships among scientists, business and government so that disconnects and conflicts among innovation, incentive and access were replaced by mutual reinforcement. Open access drug companies would spur innovation while improving the science, widening the scope and stabilizing the funding of the PPPs. They would boost R&D directed toward diseases of types II and III and develop new approaches to diseases of type I. Financial incentive would come from registering patents on track II, so that innovators would be rewarded for products that reduce the burden of disease. Companies would strive to maximize access to such products through low pricing and wide licensing.

How much should governments contribute to the incentive fund? How will governments collect reliable information on changes in burden of disease and discern which products are contributing? What about major obstacles not discussed here, such as limited ability to conduct clinical trials in less developed countries and disharmony among nations in their requirements for registering vaccines and drugs? Such challenges are manageable, in contrast to the calamitous consequences of the present course.

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