REVIEW

Assessing 15 Proposals for Promoting Innovation and Access to Medicines Globally

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ABSTRACT

Background: There is widespread recognition that the existing global systems for innovation and access to medicines need reform. Billions of people do not have access to the medicines they need, and market failures prevent new drugs from being developed for diseases that primarily affect the global poor. The World Health Organization's Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) analyzed numerous proposals for reform. The aim of this article is to build on these previous inquiries.

Methods: We conducted a structured analysis that grouped proposals into five broad opportunities for global policy reform to help researchers and decision makers to meaningfully evaluate each proposal in comparison with similar proposals. Proposals were also analyzed along three important dimensions—potential health impact, financial implications, and political feasibility—further facilitating the comparison and application of this information.

Findings: Upon analysis, no one solution was deemed a panacea, as many (often competing) considerations need to be taken into account. However, some proposals, particularly product development partnership and prizes, appeared more promising and feasible at this time and deserve further attention.

Conclusion: More research is needed into the effectiveness of these mechanisms and their transferability across jurisdictions.

Key Words: Global health, innovation, intellectual property, international development, medicines, patents, pharmaceuticals

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INTRODUCTION

In 1975, the World Health Assembly (WHA) adopted a resolution on "essential medicines" that highlighted the tragic disparities in access to lifesaving drugs around the world.[1] Almost 40 years later, these medicines remain unavailable to many people, particularly the global poor.[2] One of the greatest barriers to promoting greater access to medicines is the lack of research and development (R&D) for health products that address the diseases and conditions most affecting the world's poorest people.[2] Known as "neglected and tropical diseases" (NTDs), these ignored conditions constitute tropical or infectious diseases "for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations."[3] Some better known examples include tuberculosis, malaria, cholera, dengue fever, leishmaniasis, schistosomiasis, and yaws, yet even these receive scant attention compared with other diseases.[4] The neglect of these "diseases of the poor" is the result of both insufficient public investment and a patent system that only incentivizes companies to privately invest in drugs that can be afforded by wealthier people.[5]

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Current financing mechanisms do not provide enough incentives for the private sector to fund R&D for NTDs due to their scientific and commercial risks.[6] Current mechanisms are codified globally by the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which only provides R&D incentives for commercially attractive products.[6,7] Furthermore, the market exclusivity granted by patents and high costs of pharmaceutical R&D results in expensive drugs, making them unaffordable to the world's poor.[8-11] These conditions prevent individuals from accessing the treatments they need and deter pharmaceutical companies from investing in NTDs, severely constraining progress toward achieving global health goals.[8-10] Cumulatively, these circumstances have contributed to what many have called the "10/90 gap" in R&D financing and coordination for NTDs, where only 10% of financial investment in R&D is spent to treat 90% of the global disease burden.[12-14] To effectively address this current access gap, new strategies to manage intellectual property are needed to increase the affordability of pharmaceutical products and incentivize research into diseases that predominantly affect poorer populations.

Fortunately, after so many years, the world finally seems poised to take some action. In 2010, the 63rd WHA established a Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) to examine concerns about the lack of resources being devoted to NTDs.[15] The CEWG, building on the efforts of an earlier Expert Working Group, examined the appropriateness of various R&D financing and coordination mechanisms and the feasibility of implementing these mechanisms in the different World Health Organization (WHO) regions. The group published its final report in April 2012.[15] Additionally, further analysis was conducted and initial guidelines were informally agreed on during the 65th WHA, including subsequent special meetings to further discuss the creation of a global observatory for monitoring R&D flow, analysis of coordination mechanisms, implementation of some pilot projects, evaluation of current global financing mechanisms, and the development of proposals for a pooled and voluntary fund.[16] Following the 66th WHA, there have been stronger calls for all stakeholders to strengthen health R&D capacities and increase investments for R&D on NTDs through existing mechanisms at national, regional, and global levels.[16] Such collaboration could accelerate the development of a global health R&D observatory that would identify gaps in health R&D, or new partnerships that would facilitate product development.

These global agreements represent significant progress toward constructing a foundation to help provide affordable drugs to treat NTDs. However, it is essential for countries, industry, and institutions to cooperate and establish sustainable mechanisms that actually help address the current access gap.

To support these efforts, we reassessed the 15 most promising proposals for access to medicines reform that were considered by the CEWG. Instead of analyzing each proposal independently, we grouped them into five broad opportunities for policy reform to help global decision makers meaningfully evaluate each proposal in comparison with similar proposals. These five broad opportunities are:

1. Intellectual property reform, including patent pools, open source and precompetitive R&D, and equitable access licences;
2. Regulatory reforms, including orphan drug legislation, priority review vouchers (PRVs), and regulatory harmonization;
3. Financing reforms, including product development partnerships (PDP), tax breaks, and green intellectual property (GIP);
4. Market reform, including prizes, advance market commitments (AMC), and a Health Impact Fund (HIF); and
5. Legal reforms, including a biomedical R&D treaty (Treaty), removal of data exclusivity, and transferable intellectual property rights.

In contrast to the previous work done by the CEWG, this review presents analyses of each proposal in a structured format along three dimensions most important to global decision makers to facilitate comparison across proposals and illustrate their respective strengths and weaknesses. These three dimensions are:

1. Potential health impact, including technical feasibility, promotion of accessibility and capacity-building in developing countries, and overall public health impact in developing countries;
2. Financial implications, including value for money and the extent to which product pricing and the financing of R&D are determined independently; and
3. Political feasibility, including how powerful actors may respond to the proposal's transparency, accountability, and balance of innovation and access.

By following a structured and comparative methodology, this review builds on previous efforts to advance the understanding of these various reform proposals and presents them in an easily accessible format for researchers, health professionals, and global decision makers.

INTELLECTUAL PROPERTY REFORM

Patent pools, open source and precompetitive R&D platforms, and equitable access licences are three proposals that seek changes to the current intellectual property rights (IPR) regime to foster better R&D for medicines. The patent pool proposal uses the existing IPR regime, whereas open source and precompetitive R&D platforms seek to deviate from it. There are current projects in place which support these mechanisms,

for example, UNITAID's Medicines Patent Pool and the World Intellectual Property Organization's Re:Search; however, they are still in their early stages, making it difficult to access their effects on intellectual property reform.

Patent pools were introduced in the biotechnology sector to counter the negative effect that excessive patenting can have on innovation. The current system is known to suffer from a "tragedy of the antipatent holders" where overlapping patent rights force innovators to obtain multiple licences from multiple patent holders, thus hampering innovation.[17] Patent pools allow multiple patent holders to group their IP and jointly license their patents to each other or to a third party in a more cost-effective way.[17] Those who want to make use of a patented product may obtain licenses from this "one-stop shop" in exchange for a royalty payment set by the governing companies.[17] If patent pools are managed effectively, the drug development process should be more efficient by centralizing licensing procedures.[18]

On the other hand, open source and precompetitive R&D platforms aim to foster collaboration and encourage the sharing of ideas and information between multiple sectors by providing access to resources that may not otherwise be publicly available.[19,20] An open source R&D platform builds on the idea of online communities of researchers and scientists from industry and academia, where contributors can collectively discover new therapies for diseases. Anyone can freely use the resources and input ideas.[21] Examples include Synaptic Leap and the Tropical Disease Initiative. Unlike open source platforms, precompetitive R&D platforms are not designed to develop end-stage products. Instead, they focus on enabling technologies, highlighting promising treatments, and providing research prototypes.[22] This is achieved through sharing portfolios between multiple companies, perhaps via a joint venture or a public-private partnership.[22] Because findings are not owned by one individual company, they are described as "precompetitive." A prominent example is the European Commission's Innovative Medicines Initiative.

Equitable access licences are an alternative to the aforementioned proposals and can be seen as a compromise between patent pools and open source and precompetitive R&D platforms. This proposal focuses on reforming technology transfer agreements made between universities and private partners to ensure that the end products of publicly funded research are used in a manner that advances the public good.[23] The main aim of the scheme is to help facilitate the early entry of generic producers in low- and middle-income countries (LMICs) to drive down prices of drugs for many of the world's poorest people.[24] This scheme ensures that when a university licenses a health-related technology to a private firm, it retains the right to grant additional sublicenses for the final products and any derivatives of the initial product to a third-party generic manufacturer that would market them in LMICs.[24]

Potential Health Impact

Patent pools allow generic manufacturers to produce and distribute patented medicines before the end of a patent term, increasing the affordability of medicines in LMICs.[25] These licenses, issued for the purpose of commercialization in LMICs, result in increased competition between generic manufacturers, increasing distribution, and ultimately driving down costs for patients. Licenses can also be granted to help facilitate collaboration in developing drugs for diseases primarily affecting low-income people.[26] Some proponents have argued that patent pools can improve the safety and quality of medicines through regulated licensing.[27]

Open source and precompetitive R&D have the potential to increase the availability of medicines in LMICs, as they decrease the cost of medicines and allow for timely access to new drugs by reducing the time involved in researching new drugs.[28] However, the extent of this effect depends on the focus of the R&D. For meaningful impact on access to medicines in LMICs to occur, open source and precompetitive R&D must focus on LMIC needs, not only current market priorities.

Equitable access licences have the potential to significantly increase the affordability of drugs by driving down prices through the entry of generic products; however, such licenses fail to address gaps in R&D for neglected diseases and their delivery. The effect of equitable access licences is limited to the long-term for two reasons: 1) they can only have an impact on future drugs that are not already licensed; and 2) they target early-stage research conducted in universities, which means effects only appear many years later in drug development.[29] Under this scheme, generic companies still need to acquire the necessary licences to produce the drug, and universities still need to grant them, which further delays the effect of equitable access licences on the price of drugs and on the health of individuals in LMICs.

Financial Implications

Patent pools require minimal start-up and operating costs because they work within current patent laws, which mitigates R&D investment risks for shareholders.[18] Similarly, open source and precompetitive R&D approaches are cost-effective approaches because they do not cost much yet can facilitate collaboration thereby enabling rapid advances in a variety of activities that are, to a large extent, currently conducted independently.[28,30] By using insights from more stakeholders to predict success or failure in drug development, production costs can be lowered and funding can be channelled toward the most promising projects.[22] Open source and precompetitive R&D can also help reduce duplicative

research. Yet, without external support, neither approach currently provides sufficient financial incentives for either universities or pharmaceutical companies to invest in R&D applicable to LMICs. Equitable access licensing is also very cost-effective: Its self-implementation minimizes transaction costs for generic manufacturers wishing to supply the end products of patented research in LMICs. Equitable access licences make public research investments more cost-effective by making the end products of those investments available to a larger number of people.

Political Feasibility

Patent pools distribute the risks associated with investing in drug development and, depending on the revenue-sharing model of a patent pool, patent holders may receive a certain share of the royalties regardless of their ability to link the development of a particular medicine to their patent.[31] Patent pools present a conservative IP management strategy and can be operationalized quickly based on extensive historical precedents within existing legal structures.[17] Unfortunately, there are many obstacles associated with patent pools. Firms with potentially highly profitable drug or technology patents may be less eager to share royalties with other members: Biotechnology companies often are unwilling to expose weak patents or share ongoing research plans for which breakthroughs are expected, or voluntarily contribute their patented products if it reduces their profit margin. For a patent pool to function efficiently, patent holders have to voluntarily offer IP protected by patents into a pool and if managed improperly, this could cause anticompetitive effects, resulting in the potential for collusion and price fixing.[18,32]

Open source and precompetitive R&D require upfront costs and depend on both public and private investments to succeed. Because open source drug discovery occurs within the public domain and participants face no legal obligation to share their advances, there is the risk for participants to attempt to patent discoveries that made use of the knowledge available in open source databases, rather than making them available to others.[33] The lack of incentive to forgo IP rights makes this option unattractive to many.

Equitable access licenses contain a legally enforceable mechanism to ensure that generic producers are able to bring patented medicines to LMIC markets. A third party is required only to notify the university and patent-holding company of the need to supply a product licensed under the equitable licensing scheme in order to receive a sublicence.[34] However, the realities of university-industry technology transfers pose challenges to the successful operation of this scheme. A major challenge is getting industry partners to agree to the conditions of the licence, especially the "freedom to operate" clause, which would allow a third party to supply the patented product in any LMIC—thereby reducing the size of the market for the patent holder and creating opportunities for parallel importation of generics back to high-income countries. Industry partners also may be hesitant to grant back licences for improvements to the initial technology, especially if those improvements were costly to develop. Collective adoption of the equitable access licence by universities, however, could significantly increase their bargaining power in this respect.

REGULATORY REFORM

Orphan drug acts (ODAs), PRVs, and regulatory harmonization are three proposals for regulatory reform that address the need to stimulate and coordinate greater commitment to treating NTDs.

"Orphans drugs" are medicines that treat rare diseases affecting less than 200,000 people.[35,36] The ODA proposal offers incentives which differ from the current "blockbuster" model. Rather than having a company place all of its resources toward a potential drug that can be sold to millions of people, ODAs set up a premium-pricing model for new, smaller-market drug therapies. The benefit of ODAs is that pharmaceutical companies are given market exclusivity, and there are established mechanisms to prevent others from developing a competing drug.[37] However, in order for companies to take advantage of this incentive, the holders must "assure the availability of sufficient quantities of the drug to meet the needs of persons with disease" as well as prove the effectiveness of the drug.[38] This ensures that the drug can be developed and brought to market and can meet the demand of the small population.

The PRV system offers expedited review to allow drugs to reach the market quicker. This allows companies to start earning profit sooner and benefit from their patent-protected monopolies for longer.[39] With PRVs, when a treatment for an NTD receives FDA approval, not only does that drug go through a fast-track approval process, the pharmaceutical company is also given a voucher that allows another one of its drugs to benefit from expedited review as well. This voucher can be sold or transferred to other parties by the PRV holders, making it potentially worth many millions of dollars.[40]

Regulatory harmonization encompasses any regulatory reform aimed at improving current efforts in drug development such as developing universal procedures for research, development, and approval; streamlining procedures to reduce their burden on governments, applicants, and regulatory agencies; and improving systems of information-sharing between companies and stakeholders.[41,42]

Potential Health Impact

Since its launch, the ODA has been successful in stimulating R&D of orphan drugs in the United States. Prior to its enactment in 1983, only 10 orphan drugs were marketed; now more than 200 orphan drugs have been approved by the FDA.[36] ODA provides extended market

exclusivity rights and tax credits to companies that develop an orphan drug, which ensures that the drug firms reap the rewards for their investment in orphan drugs through a premium-pricing model for new, smaller-market drug therapies. In addition, the ODA provides an element of protocol assistance during the research stages, providing firms with free scientific advice in regards to their drug's quality, safety, and efficacy. Protocol assistance can help drug firms manage their resources more wisely and speed up the approval process.[43]

The PRV proposal also offers an incentive to invest in R&D for NTDs; however, proposals generally limit eligibility to treatments that include entirely novel ingredients.[40] This could constructively facilitate a race to discovery or, alternatively, deter pharmaceutical companies from investing in R&D for NTDs in fear of coming second.[44]

The goal of regulatory harmonization is to streamline and promote international expansion and increase the availability of medicine, especially for NTDs. By providing a platform and universal regulation to R&D, it can help create efficiencies, speed up the process for drug approval, and quicken the production of these medicines and sale to market. In doing so, regulatory harmonization could increase the supply of NTD drugs while decreasing the administrative cost, thereby improving the affordability and availability of these drugs.[45] However, regulatory harmonization does not address the total pool of financing available for NTD R&D.

Financial Impact

Though potentially profitable, implementation of the ODA proposal in other jurisdictions could be a double-edged sword for drug firms. While the "winner takes all" model secures the victor's ability to market its drug free of competition, the same model results in wasted time and resources that competing firms may have spent developing similar drugs. Therefore, as market exclusivity creates a secure monopoly, it could discourage other drug firms from working on the development of drugs for the same orphan diseases.[46] In addition, this new premium-pricing model aims to target patients with unique disease characteristics, which will increase the cost of these drugs, as they specifically target a group of patients who need to take these drugs in order to survive, creating another monopoly in the system.

In the PRV scheme, public sector authorities do not incur extra costs or resources, nor is there financial input from taxpayers; instead, voucher holders actually pay a user fee which covers any extra costs for the expedited review.[40] The voucher is nonetheless an attractive financial incentive, especially for large pharmaceutical companies, as the user cost would be minimal in comparison to the potential profit gained from earlier time to market.[47] Smaller biotechnology companies could offset costs of investing in R&D for an NTD through the sale of a voucher.[48] PRV could also benefit consumers, who would receive medicines earlier.[39] Unfortunately, due to the market-driven nature of vouchers, it is difficult to estimate their true value. Many of the high-value estimates of vouchers are based on projections of the sales of blockbuster drugs, whereas the actual value of a voucher is product-specific. Other factors, such as the likelihood of being granted a priority review without a voucher and the unknown profit from earlier entries to market, also affect the value of a voucher.

Despite an increase in pharmaceutical resources and funding, there has been a decrease in annual numbers of new active substance approvals.[49] Harmonization aims to reduce fragmented and overlapping R&D efforts by streamlining and standardizing processes within the pharmaceutical R&D sector.[42,50] The goal is to achieve more productive R&D for money spent. Harmonization could strengthen the system by focusing on collaborations, which could promote timelier and more cost-effective market entry of drugs, thereby reducing prices for consumers.[50,51] While regulatory harmonization could strengthen coordination among actors and lower R&D costs, it does not necessarily incentivize innovation.

Political Feasibility

In terms of its political attractiveness, subsidization of R&D, market exclusivity, and protocol assistance have attracted support from pharmaceutical companies for the ODA because it allows pharmaceutical companies to still benefit from market monopolies while also receiving public assistance. Key stakeholders are likely to support implementation of the proposal, as it encourages the development of drugs that target rare diseases with relatively small public costs. Patients and families affected by different orphan diseases have also proven to be a formidable lobby. However, since ODA does not address improvements for access to the medicines or guarantee that drug prices will be lowered, many patient advocate groups and developing countries have expressed reservations about this proposal because it seems like another opportunity for companies to gain a monopoly on the sale of their products.[52]

The PRV proposal is consistent and complementary to existing incentive mechanisms, making it more politically feasible; however, it fails to address IP management aside from the fact that the voucher could allow companies to bring their products to market earlier and effectively extend their market monopoly. PRVs help to facilitate the competition of ideas, but without any coordination system, it allows the current overlaps in drug development to continue. One major concern associated with this proposal is that it fails to address the implementation of therapy after a PRV has been rewarded. If new effective drugs are developed but not administered, the ultimate goal of treating people with NTDs will not be met.

While regulatory harmonization of pharmaceuticals has many advantages, there are concerns regarding its implementation. The ability of a country to regulate the entry of new drugs is determined by several factors, including economic development, infrastructure, policy capacity, health system arrangements, and, perhaps most importantly, the financial and human resources available for governmental regulation.[53] Unfortunately, many developing countries lack sufficient resources to ensure the quality and safety of drugs.[53,54] For this mechanism to be feasible, agencies like the FDA and WHO could play a greater role in setting norms and standards for the quality assurance of medicines for national and international markets, as well as assist countries to build their regulatory capacity.[53]

FINANCIAL REFORM

Currently, health R&D is funded publically by research councils and privately by a combination of shareholder equities in pharmaceutical companies and internally generated revenues.[12] Financial reform proposals help address the need for greater cooperation between the public and private sector. PDPs, tax breaks and grants, and GIPs are three avenues to address sustainable funding of R&D for medicines.

PDPs bring together public-sector funding and private-sector resources and direct both toward a common goal through pooled funding.[9] The CEWG analyzed three different PDP pooling mechanisms: 1) PDP financing facility; 2) an Industry R&D Facilitation Fund (IRFF); and 3) a Fund for Research in Neglected Diseases. A PDP financing facility is a bond-financed pooled fund to support long-term PDP development in R&D for NTDs.[41] These are legally binding commitments made by donor countries and private entities with high credit ratings, which would repay bondholders in the event of financial shortfalls.[55] This allows bonds to be issued by multilateral development banks on international capital markets, relaying proceeds to finance PDP activities through royalties, premiums, and grants.[55] An IRFF is a separate pooled fund, which can be created to finance PDPs with approved plans for R&D in NTDs.[56] Donors invest in a portfolio of PDPs, creating a central financial hub and thus requiring recipients of funding to meet strict eligibility criteria and pass periodic progress reviews to receive continued support.[56] IRFFs commit to a PDP funding ceiling for 5 years based on equivalent donor commitments.[57] Finally, a Fund for Research in Neglected Diseases creates a pooled fund specific to R&D for NTDs, applying portfolio management techniques to allocate funds on a milestone-to-milestone approach to select the best drug candidates for NTDs.[58]

Tax breaks generally refer to tax deductions or refundable credits provided by governments after processing the company's claim on R&D expenditures. Providing grants in the initial phases of research with tax credits could offer additional incentives, improving the current financing system for R&D in NTDs.[59]

GIPs divert part of the patent-related monetary flow toward a trust fund used to finance R&D for NTDs.[60-62] A compulsory tax is collected at three stages: 1) assurance premiums on patent applicants; 2) patent owners; and 3) an allocation of fees collected by patent officers.[61] There are also two distinct mechanisms of financing GIPs: aid and insurance. Aid aims to finance access to technologies by providing grants to countries for costly patent licenses and to organizations for direct drug purchases.[12] On the other hand, by subsidizing the cost of the licensing fee, GIP insurance allows for the non-commercial transfer of patents from pharmaceutical companies to users who are unable to access technologies due to lack of capital.[62]

Potential Health Impact

An additional fund of at least $1 billion USD annually will be required over the next decade to fund R&D for NTDs[63]; therefore, allocating available funds wisely is a critical step.[63] The milestone-to-milestone funding approach proposed as part of a Fund for Research in Neglected Diseases could spur innovation while limiting financial risk. The "partial portfolio management" strategy allows innovation during early stages of R&D and optimizes fund allocation.[57] These strategies ensure that only promising projects are funded and that monetary resources are not wasted. Similarly, GIPs ensure that funds are allocated only to projects with the greatest necessity based on attempted IP negotiations between patent users and holders, to encourage affordable transfers of technology.[60] Grants are assigned to projects with the greatest potential for innovation[64,65]; however, the allocation assessment process is not uniform and is subject to personal biases.[15,66]

The minimal changes in status quo for pharmaceutical companies within tax breaks and grants make this proposal politically feasible. Funds for NTD research and IRFFs are less likely to appeal to stakeholders, given the limited incentive for major investors to participate in pooled funds. The novelty and complex system of the GIP system detracts from its political appeal. In general, new taxes are politically unfavorable and unlikely to generate popular support.[56]

Financial Impact

PDP financing facilities offer the most inventive source of funding by tapping into capital markets. This occurs through bond issuances offered by a multilateral development bank and the most diverse funding options.[55] Similar to financing facilities, GIP draws on a new market to fund a trust to finance R&D for NTDs. It introduces a new "tax" that innovatively draws on the monetary flow of the global IP system.[15,67] GIP taxes are flexible and can be adjusted to local contexts to promote dependable funding and encourage participation among

low-income countries.[68] Tax breaks and grants offers little innovation because they merely couple two existing R&D funding mechanisms.[59] The funds within PDP are designed and implemented to specifically fund R&D for NTDs.[57] In contrast, tax breaks and GIPs do not guarantee that full proceeds will be directed to R&D for NTDs, because they are marked for R&D expenditures in general.[60,69]

IRFFs are the most cost-effective because they require the least investment.[56] Tax breaks also have low management costs because companies already pay their own administrative fees to claim tax incentives.[70] Estimates for initial expenses for a PDP financing facility range from low to modest depending on bond issuance costs[57,67]; however, the model projects significant long-term revenue,[55] making it relatively cost-effective. Funds for NTD research would incur significant costs due to their milestone-to-milestone funding allocation strategy. GIPs would also require significant upfront and ongoing investment costs as tax introductions require legal changes and consistent regulations to ensure compliance.[15]

PDP financing facilities are designed to be self-sufficient once established, attracting supports of sustainability. Front-loaded funding for 10 to 15 years through bonds and donor guarantees allows LMICs and PDPs to plan longitudinally, knowing the exact availability of resources. GIP funding schemes rely on taxation that is both financially sustainable and relatively predictable. Global taxes are not likely to be affected by economic downturns. However, there is only moderate certainty over revenue forecasts, as actual revenues will depend on providers' and consumers' responses to the new tax and offer little predictability.[70,71]

Political Feasibility

Global financing mechanisms require robust governance structures that are centrally operated to effectively manage and allocate resources.[57,72] Both PDPs and GIP require an external governing body to manage and allocate the resources: PDPs employ various independent, small governing bodies, whereas GIP is governed by one central body, the proposed being the World Trade Organization (WTO).[57,62] If the WTO becomes the governing body, little will change in the current system, as the current WTO Trade-Related Aspects of Intellectual Property Rights Agreement is a key basis of international patent law, thus rendering minimal change to making drugs more affordable or promoting innovation. In contrast, tax breaks do not require new formalized governance structures and can be implemented in government's existing taxation programs.[70] One mechanism which makes GIP taxes favorable is their flexibility, as they can be adjusted to local contexts to promote dependable funding. This is more likely to garner support from LMICs because it could allow them to develop their own R&D infrastructures, which hopefully allows them to develop drugs at prices more affordable to their citizens.[68] However, GIPs are taxes, and any tax increases would be seen as politically unfavorable.

PDPs provide funding to the most promising projects to ensure that resources are not wasted; however, as PDPs rely heavily on external funding, the allocation of funds may depend on donor agreement rather than which project represents the most promising use of funds from a health impact or feasibility perspective.

There are currently different forms of tax breaks and grants geared toward getting pharmaceutical companies and research institution to invest in R&D for NTDs; however, there is conflicting evidence on whether yet another incentive would actually encourage these actors to break away from their current practices.[59] Overall, even though these financial mechanisms aim to raise more money and channel it into R&D for NTDs, LMICs may not be able to sustain the introduction of complex financing mechanisms.[70]

MARKET REFORM

Some proposals catalyze market reforms to reduce the current access gap for medicines. Prizes, AMCs, and the HIF are three such proposals.

Prizes are monetary rewards that, in this case, encourage the development of drugs for neglected diseases.[3] The aim of such incentives is to delink the cost of the product from its development.[73] Sponsors establish competitions, offering rewards to developers who can design and execute predefined target products.[3] In exchange for accepting prizes, drug developers relinquish their IPRs, allowing for generic manufacturing of the drugs and thus lowering the cost of the drugs.[3] There are two types of prizes: End prizes are awarded at the final stage of a product's development, and milestone prizes are awarded at intermittent points along the development pathway.[3]

AMCs are legally binding preorder contracts that are made between pharmaceutical developers and funders.[74] Sponsors of AMCs guarantee the future purchase of drugs that are currently in their developmental stages; in exchange, developers agree to supply a set amount of their completed products at a set price.[74] For each AMC, an independent adjudication committee is established to determine if finished products meet a designated product profile.[75] Costs of AMCs are shouldered mainly by donors (e.g., high-income countries) but a smaller "copay" can be paid by low-income countries who seek to benefit from them.[75] After the initial amount of the drug has been delivered and paid for, developers then provide their products for a previously negotiated "tail-price."[76]

HIF is a pay-for-performance scheme that remunerates developers based on the health impact of their drug.[77] If companies choose to register with the HIF, developers are required to sell their products at cost. In exchange, they receive an annual share of rewards from a

fixed pool of money that is proportional to their product's health impact.[77]

Potential Health Impact

In recent years, prizes have found success in promoting smaller-scale innovations[78,79]; however, they remain unproven in the context of drug development.[73] End prizes do little to compensate for the risks of early stage R&D.[3] Milestone prizes address this concern by providing rewards at intermittent points along the development pathway, allowing investors to funnel prize money back into the R&D process and reducing their financial risk.[3] Unfortunately, once a prize has been paid and a drug has been brought to market, there are no continual incentives to improve on existing products.[3,73] Prizes also fail to address drug distribution (at least as most often proposed).

AMCs can be used to stimulate R&D for drugs at all stages of development[76]; however, the ability of AMCs to promote early stage R&D still remains largely theoretical. AMCs aim to create a market for drugs in their early stages of development by establishing contracts between developers and purchasers,[80] guaranteeing the purchase of products for NTDs. Additionally, purchasers will only allow a product to enter into an AMC if the product is clinically superior to an existing drug,[76] incentivizing developers to improve on existing products. Similar to prizes, AMCs do not encourage effective distribution of medications.[76]

The attractiveness of HIF lies in its ability to offer lucrative payouts for drugs that would otherwise be unprofitable under the current patent system.[77] The payouts are anticipated to be large enough to generate investment at both early and late-stage development.[77] Similar to AMCs, HIF offers continual incentives for companies to improve on existing treatments by rewarding drugs with greater health impact.[77] HIF also addresses low drug costs and ensures effective drug distribution to target populations.[77]

Prizes have been criticized for the complexity of the administrative structures required[3]; nevertheless, they are versatile and can be implemented within the current pharmaceutical market.[3,73] Major challenges of operationalizing AMCs revolve around the multiplicity of actors involved and the complexity of their administrative structure, which detracts from its feasibility. HIF suffers from similar issues, as it requires a considerable amount of personnel and an administrative budget of up to $600 million USD annually.[77] Furthermore, there are also complications with the data collection process and the utilization of the quality-adjusted life-year scale to measure health.[81]

Financial Impact

Incentivizing mechanisms for R&D require a large operating budget and in their current forms, none of the proposals include self-sustaining funding mechanisms or a reliable source of donor money. In the current pharmaceutical market, prizes appear to be the easiest to implement but seem unlikely to draw donor and developer support. Although AMCs are more difficult to implement and require the creation of new governance structures, past evidence suggests that they appeal to major stakeholders and are attractive to both donors and developers. HIF's pay-for-performance scheme and the $600 million USD annually required for funding may make it unattractive to donors and developers alike.

Political Feasibility

Drug developers can be disinclined to participate in the prize scheme because of the "winner-takes-all" quality and the requirement that developers forfeit their IP upon receiving a reward.[73,82] Also, donors fear the potential overpayment of R&D, as prizes are set before R&D and are based on estimates.[3] Additionally, because milestone prizes reward innovation before products have reached fruition, donors run the risk of awarding prizes for products that never reach the market.[3,73] In the AMC scheme unlike prizes, donors only pay for finished products. The drawback however is that in early stage development, the costs, risks, and potential returns of R&D investments cannot be accurately estimated.[83] AMCs and HIF on this front are both favourable to drug developers because the schemes help reduce drug prices while allowing developers to retain their IP.[77,84] HIF's biggest challenge, however, is convincing developers to invest money into R&D for NTDs because firms need to be confident that their remuneration mechanism has proven reliable.

LEGAL REFORM

The pharmaceutical industry has been responsible for most contemporary medical innovations; however, the current model of R&D that is incentivized by patents has been challenged.[85] The adoption of a treaty, the removal of data exclusivity, and transferable intellectual property rights (TIPR) are three schemes that look to transform the current R&D environment through changes in the law governing health R&D.

A biomedical R&D treaty would be an international legally binding agreement among states. The treaty would have four key tenets: 1) ensuring sustainable investment in medical innovation; 2) providing fair allocation of the cost burdens of innovation; 3) creating mechanisms to drive R&D investment toward areas of greatest need; and 4) providing the flexibility to use diverse and innovative methods of financing pharmaceuticals while ensuring access and protection for consumers.[86-88] The treaty could also help establish global norms to promote sustainable financing for R&D and the management of intellectual property.[86,88]

Before data exclusivity, generic pharmaceutical companies were permitted to use innovators' clinical trial

data when submitting products for market approval[89]; however, with data exclusivity, generic companies can no longer use innovators' data for a set period of time. Removing data exclusivity will allow generics to gain earlier approval from regulatory bodies and prepare in advance for distribution so that medicines can be made available at cheaper standard prices immediately on expiry of relevant patents.[90,91]

TIPR aims to address the lack of development and investment for neglected diseases. TIPR allows a company to receive a patent extension on a drug of their choice in exchange for developing a drug or vaccine for a neglected disease.[85,92] The goal is to greatly reward high-impact, complex, and innovative solutions. Low-impact or easy discoveries would receive smaller patent extensions, thus encouraging companies to work on difficult issues.[93]

Potential Health Impact

The treaty proposal aims to create a stronger partnership among companies, national governments, and international organizations to allow them to harness their expertise and develop new treatments and cures for diseases that primarily affect the poor.[89,94] A proposed requirement of the treaty is that in order to receive funding, products are to be more effective than what is currently available on the market—thereby ensuring that any new health products have a real impact.[86,95-98] Removing data exclusivity allows companies in developing countries to increase production and the availability of pharmaceuticals in a shorter time frame.[90] Without data exclusivity, governments are able to fund local generic pharmaceutical companies to manufacture and distribute necessary medicines, rather than importing them, further increasing availability and affordability.[99] TIPR aims to affect health in developing countries by extending preexisting patents of a company's choice based on another new drug's ability to treat NTDs.[93] The model only rewards development of pharmaceuticals while doing little to increase their delivery.[93] However, proposals for this scheme do not provide enough detail about how the mechanisms would work nor does it address the long-term goal of increasing R&D capacity in developing countries. Nevertheless, this proposal does provide opportunities for small biotechnology firms, who have innovative ideas but may lack capital and cannot proceed with trials.[85,93]

Financial Impact

National government involvement is important for the treaty, as the government would bear the responsibility for its adoption and initial costs.[89,94] Governments are not restricted by profit imperatives and as such can perhaps better ensure that money is funnelled into high-impact initiatives. The treaty shifts the monetary responsibility and risks for some research away from companies and onto national governments, thereby making R&D a global public good.[86,88,96-98] However, the treaty is expensive and calls for countries to contribute 1% of their gross domestic product in order to delink the cost of R&D from product prices.[86,98] Removing data exclusivity would decrease revenues for innovators and could have negative effects on innovation by weakening their ability to recover the costs of R&D.[85] Nonetheless, removing data exclusivity would create more market competition by increasing the number and amount of drugs in the market, resulting in lower prices for consumers.[100,101] Under the TIPR scheme, costs of NTD R&D do not need to be recouped through the sale of the final NTD product, allowing the price of the drugs for NTDs to be set at or below costs.

Political Feasibility

The treaty could weaken IP management overall by creating an alternative system to patents that would have free dissemination of information.[86,89,94,97,98] Similarly, the removal of data exclusivity would be a reversal to the global trend of strengthening IP law, which would attract opposition from the pharmaceutical industry and private sector. However, TIPR could work within the existing IP system and extend the monopoly on a pharmaceutical companies' "drug of choice," presumably a drug targeting wealthy populations in developed countries.[85,93]

The treaty calls for a rebalancing of decision-making processes, increasing the role of national governments—particularly those of emerging countries.[86,95,97,98] However, this is difficult for developing countries to do and parts of this proposal may be unfavorable to industry.[86,95,98,102] The removal of data exclusivity would negatively affect the profits of many pharmaceutical companies[103] and the proposal does not provide them any incentive to recuperate their R&D costs. Despite its unattractiveness to governments, innovators find TIPR to be very attractive, as it would increase the patent life of their most profitable products and increase value for their shareholders.

DISCUSSION

The current state of global health recognizes the urgency to address the health needs of people in developing countries, especially the inequities related to R&D of NTDs, which are due to market failures. However, in today's global society, there are many stakeholders in health R&D and this has led to a disorganization of health research, especially those pertaining to NTDs. Thus mechanisms are needed to improve coordination and financing of health R&D. Certain proposals analysed by the CEWG, such as equitable access licences, focus on improving the cooperation, participation, and coordination of health R&D. Proposals like PDPs and prizes focus on overcoming market failures, which would provide stakeholders financial incentives to develop medicines for LMICs. The CEWG has suggested four fundamental

ideas for a new R&D system, which include: 1) free open market competition in production; 2) delinking R&D costs and the price of product; 3) upfront public financing of R&D; and 4) re-establishing R&D as a global public good.[53] The treaty proposal is put forward as a way to establish a new R&D system based on these four fundamental principles. As the current proposal is vague, different stakeholders would decide what mechanisms should be adopted and those that should be bound by law.

Based on this analysis of these 15 proposals, it is clear that none could stand alone as the solution to a new health R&D system. However, several mechanisms integrated together could offer a very good foundation for a more effectively coordinated and financed health R&D system that would ensure both innovation and access to health products for NTDs.

CONCLUSION

Until now, patents and the protection of IP that they offer have been the main way through which inventors and investors have been incentivized to conduct health R&D. However, this market exclusivity has led to high costs of health products, making them inaccessible to the world's poorest people.[104] The current system provides few incentives for investments in health R&D on diseases that primarily affect LMICs. The WHO created the CEWG to help find ways to address the status quo. The CEWG analyzed many promising proposals submitted by various stakeholders, which address new coordination and financing mechanisms to encourage more R&D for NTDs.

The CEWG recognized that there is a need to improve monitoring of health R&D resource flows and identification of gaps in health R&D, through the establishment of a Global Health R&D Observatory. However, the observatory alone does not provide adequate coordination, sustainable financing, or production of new medical innovations. More research and open-ended discussions at national and global levels are necessary to establish new coordination and financial mechanisms. Comparing and contrasting existing proposals, as done here, represents an important start.

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References

1. World Health Organization. WHA28.66: prophylactic and therapeutic substances. Geneva: World Health Organization. Available at: http://apps.who.int/medicinedocs/documents/s21447en/s21447en.pdf; 1975. Accessed April 12, 2015.
2. Quick JD, Hogerzeil HV, Velazquez G, Rago L. Twenty-five years of essential medicines. Bull World Health Organ 2002;80:913–4.
3. Maurer SM. The Right Tool(s): Designing Cost-effective Strategies for Neglected Disease Research. Berkeley, CA: Goldman School of Public Policy; 2005.
4. Røttingen JA, Regmi S, Elde M, et al. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? Lancet 2013;382:1286–307.
5. TDR. Monitor, evaluate, improve: TDR results 2012 report. Available at: http://apps.who.int/iris/bitstream/10665/85301/1/TDR_STRA_13.2_eng.pdf; 2012. Accessed April 12, 2015.
6. Trouiller P, Torreele E, Olliaro P, et al. Drugs for neglected diseases: a failure of the market and a public health failure? Trop Med Int Health 2001;6:945–51.
7. Van Puymbroeck RV. Basic survival needs and access to medicines—coming to grips with TRIPS: conversion + calculation. J Law Med Ethics 2010;38:520–49.
8. Bhalla A, Suri V, Malhotra S. Patents on therapeutics in developing countries: the challenges ahead. Expert Opin Ther Pat 2007;17:1015–25.
9. Grace C. Product development partnerships (PDPs): lessons from PDPs established to develop new health technologies for neglected diseases. Oxford, UK: Human Development Resource Centre; 2010.
10. Cohen-Kohler JC, Forman L, Lipkus N. Addressing legal and political barriers to global pharmaceutical access: options for remedying the impact of the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and the imposition of TRIPS-plus standards. Health Econ Policy Law 2008;3:229–56.
11. Grover A, Citro B, Mankad M, Lander F. Pharmaceutical companies and global lack of access to medicines: strengthening accountability under the right to health. J Law Med Ethics 2012;40:234–50.
12. Hecht R, Wilson P, Palriwala A. Improving health R&D financing for developing countries: a menu of innovative policy options. Health Affairs 2009;28:974–85.
13. Stiglitz J, Jayadev A. Medicine for tomorrow: some alternative proposals to promote socially beneficial research and development in pharmaceuticals. J Generic Med 2010;7:217–26.
14. Loff B, Heywood M. Patents on drugs: manufacturing scarcity or advancing health? J Law Med Ethics 2002;30:621–31.
15. World Health Organization. Consultative Expert Working Group on Research and Development: Financing and Coordination. Geneva: WHO; 2011.
16. World Health Organization. Follow up of the report of the Consultative Expert Working Group on Research and Development: Financing and coordination 2013 May p. 4. Report No.: WHA 66.22. Available at: http://www.who.int/phi/resolution_WHA-66.22.pdf. Accessed April 12, 2015.
17. Clark J, Piccolo J, Stanton B, Tyson K. Patent Pools: A Solution to the Problem of Access in Biotechnology Patents. Alexandria, VA: US Patent and Trademark Office; 2000.
18. Bermudez J, 't Hoen E. The UNITAID patent pool initiative: bringing patents together for the common good. Open AIDS J 2010;4:37–40.
19. Berends H, Bij H, Debackere K, Weggeman M. Knowledge sharing mechanisms in industrial research. R&D Management 2006;36:85–95.
20. Flynn S, Hollis A, Palmedo M. An economic justification for open access to essential medicine patents in developing countries. J Law Med Ethics 2009;37:184–208.
21. Napa J. Open source drug discovery: a feasible business model? Available at: http://www.pharmafocusasia.com/strategy/open_source_drug_discovery.htm. Accessed April 12, 2015.
22. Nwaka S, Ridley RG. Virtual drug discovery and development for neglected diseases through public-private partnerships. Nat Rev Drug Discov 2003;2:919–28.
23. Godt C. Equitable licenses in university-industry technology transfer. Available at: http://www.med4all.org/fileadmin/med/pdf/Godt_Equit_Lic_GRUR_Int_20111_377_385.pdf. Accessed February 10, 2015.
24. Kapczynski A, Chaifetz S, Katz Z, Benkler Y. Addressing global health inequities: an open licensing approach for university innovations. Berkeley Technol Law J 2005;20:1031.
25. Stirner B. Stimulating research and development of pharmaceutical products for neglected diseases. Eur J Health Law 2008;15:391–409.

26. Sukkar E. Patent pools: an idea whose time has come. BMJ 2009;338:b1630.
27. Satyanarayana K, Srivastava S. Patent pooling for promoting access to antiretroviral drugs (ARVs)—a strategic option for India. Open AIDS J 2010;4:41—53.
28. Masum H, Harris R. Open Source for Neglected Diseases: Magic Bullet or Mirage?. Washington, DC: Results for Development Institute; 2011.
29. Giaccotto C, Santerre RE, Vernon JA. Drug prices and research and development investment behavior in the pharmaceutical industry. J Law Econ 2005;48:195—709.
30. Frankort HTW, Hagedoorn J, Letterie W. R&D partnership portfolios and the inflow of technological knowledge. Industrial and Corporate Change 2012:507—37.
31. Layne-Farrar A, Lerner J. To join or not to join: examining patent pool participation and rent sharing rules. Int J Indust Organ 2011;29:294—303.
32. Barpujari I. Facilitating access or monopoly: patent pools at the interface of patent and competition regimes. JIPR 2010;15:345—56.
33. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of health development costs. J Health Econ 2003;2:151—85.
34. Chaifetz S, Chokshi DA, Rajkumar R, Scales D, Benkler Y. Closing the access gap for health innovations: an open licensing proposal for universities. Global Health 2007;3:1.
35. World Health Organization. First WHO Report on Neglected Tropical Diseases: Working to Overcome the Global Impact of Neglected Tropical Diseases. Geneva, Switzerland: WHO Press; 2010.
36. U.S. Food and Drug Administration. Developing products for rare diseases & conditions. Available at: http://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/default.htm; 2011. Accessed April 12, 2015.
37. Reaves ND. A model of effective health policy. J Health Soc Policy 2003;17:61.
38. U.S. Food and Drug Administration. Orphan Drug Act. Public Law 97—414, October 2011. Available at: http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/orphandrugact/default.htm. Accessed April 12, 2015.
39. Grabowski HG, Ridley DB, Moe JL. Priority review vouchers to encourage innovation for neglected diseases. In: Eggleston K, ed. Prescribing Cultures and Pharmaceutical Policy in the Asia-Pacific. Washington, DC: Brookings Institution Press; 2009, pp 347—66.
40. U.S. Food and Drug Administration. Priority review to encourage treatments for tropical diseases. Section 524, Federal Food, Drug, and Cosmetic Act. Available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/ucm110316.htm; April 2009. Accessed April 12, 2015.
41. De Renzio P, Booth D, Rogerson A, Curran Z. Incentives for Harmonisation and Alignment in Aid Agencies. London, UK: Overseas Development Institute; 2005.
42. Harmonization, Alignment, Results: Report on Progress, Challenges and Opportunities. Paris (France): OECD-DAC Working Party on Aid Effectiveness; 2005.
43. Shah R. Regulatory framework for the treatment of orphan diseases. In: Mehta A, Beck M, Sunder-Plassmann G, eds. Fabry Disease: Perspectives from 5 Years of FOS. Oxford, UK: Oxford PharmaGenesis; 2006.
44. Kerin RA, Varadarajan PR, Peterson RA. First-mover advantage: a synthesis, conceptual framework, and research propositions. J Marketing 1992 Oct;56:33—52.
45. World Health Organization. The World Medicines Situation. Geneva, Switzerland: World Health Organization; 2004.
46. Gottlieb J. Orphan drugs: future viability of current forecasting models, in light of impending changes to influential market factors [Master's thesis]. Cambridge, MA: Massachusetts Institute of Technology; 2011.
47. Hollis A, Pogge T. The health impact fund: making new medicines accessible for all [Internet]. New Haven, CT: Incentives for Global Health; 2008.
48. Noor W. Placing value on FDA's priority review vouchers. In Vivo: The Business & Medicine Report 2009;27:1—8.
49. Gostin LO, Mok EA. Grand challenges in global health governance. Br Med Bull 2009;90:7—18.
50. ICH Official Website. Geneva, Switzerland: International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
51. Shanley A. Taking the plunge to harmonize pharmaceutical regulations. PharmaManufacturing. Available at: http://www.pharmamanufacturing.com/articles/2010/034.html. Accessed April 12, 2015.
52. Kaiser Public Opinion Spotlight. Views on prescription drugs and the pharmaceutical industry. Available at: http://www.kff.org/spotlight/rxdrugs/upload/Rx_Drugs.pdf; 2008. Accessed April 12, 2015.
53. CEWG Final Report World Health Organization. Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination. Consultative Expert Working Group on Research and Development: Financing and Coordination; 2012 Apr p. 226. Available at: http://www.who.int/phi/CEWG_Report_5_April_2012.pdf?ua=1. Accessed April 12, 2015.
54. World Health Organization. The Impact of Implementation of ICH Guidelines in Non-ICH Countries. Geneva, Switzerland: World Health Organization; 2002.
55. International AIDS Vaccine Initiative. Financing the accelerated development of vaccines for AIDS, TB, and malaria: design of the PDP financing facility and an analysis of its feasibility—a report to Aeras, IAVI, and MVI. 2009 Feb. 40 p.
56. Moran M, Ropars AL, Guzman J, Diaz J, Garrison C. The New Landscape of Neglected Disease Drug Development. London: Wellcome Trust; 2005.
57. Grace C, Pearson M, Lazdins J. Pooled Funds: Assessing New Models for Financing Global Health R&D. Washington DC: Results for Development Institute; 2011.
58. Herrling PL. Making drugs accessible to poor populations: a funding model. Global Forum Update on Research for Health 2008;5:152—5.
59. Rao A. R&D Tax Credits: A Tool to Advance Global Health Technologies?. Washington DC: Centre for Global Health R&D Policy Assessment; 2011.
60. Nitta I. Patents and essential medicines: an application of the Green Intellectual Property project. Geneva, Switzerland: Institut de Hautes Etudes Internationales et du Developpement; 2007.
61. Nitta I. International fund for innovation: an innovative financing mechanism for medicines in the developing world. Geneva, Switzerland: Institut de Hautes Etudes Internationales et du Developpement; 2006.
62. Nitta I. Green Intellectual Property scheme: a blueprint for the eco/socio-friendly patent framework. Geneva, Switzerland: Institut de Hautes Etudes Internationales et du Developpement; 2006.
63. Herrling PL. Financing R&D for neglected diseases [editorial]. Nat Rev Drug Discov 2009;8:91.
64. International AIDS Vaccine Initiative. IAVI's innovation fund to bring novel early-stage technologies to AIDS vaccine research: flexible and rapid-response funding for pioneering ideas. New York; [no date]. Available at: http://r4d.dfid.gov.uk/PDF/Outputs/iavi/iavifactsheetinnovation.pdf. Accessed April 12, 2015.
65. De Ferranti D, Griffin C, Escobar ML, Glassman A, Lagomarsino G. Innovative Financing for Global Health: Tools for Analyzing the Options. Washington DC: Brookings Global Economy and Development; 2008.
66. Martin B. Research grants: problems and options. Austral Univ Rev 2000;43:17—22.
67. Fryatt R, Mills A, Nordstrom A. Financing of health systems to achieve the health Millennium Development Goals in low-income countries. Lancet 2010;375:419—26.
68. Moon S. Medicines as Global Public Goods: The Historical Evolution of and Contemporary Debates on Technological Innovation for Global Health [working paper]. Cambridge, MA: Harvard University Press; 2009.
69. Organization for Economic Co-operation and Development. Tax Incentives for Research and Development: Trends and Issues. Paris, FRANCE: Organization for Economic Co-operation and Development; 2002.
70. Tax Memo 2005-2006. London: FL Memo Limited; 2005.
71. Public Health, Innovation and Intellectual Property: Report of the Expert Working Group on Research and Development Financing. Geneva, Switzerland: World Health Organization; 2009. Report No. EB126/6 Add.1.

72. Fidler DP. The Challenges of Global Health Governance. New York, NY: Council on Foreign Relations Press; 2010.
73. Sonderholm J. Intellectual Property Rights and the TRIPS Agreement: An Overview of Ethical Problems and Some Proposed Solutions. Washington DC: The World Bank Development Research Group; 2010. Report No. 5228.
74. Subramanian A. People in economics: harnessing ideas to idealism on Michael Kremer. Fin Dev 2007;44:1–57.
75. Hollis A. A Comprehensive Advance Market Commitment: A Useful Supplement to the Patent System?. Calgary, Alberta, Canada: Department of Economics, University of Calgary; 2007.
76. Levine R, Kremer M, Albright A. Making Markets for Vaccines: Ideas to Action. Washington DC: Center for Global Development; 2005.
77. Hollis A, Pogge T. The Health Impact Fund: Making New Medicines Accessible for All. New Haven, CT: Incentives for Global Health; 2008.
78. Prizes and programs: biomarker prizes. Berkely, CA: Prize4Life Inc; 2010. Available at: http://www.prize4life.org/page/prizes/biomarker_prize. Accessed April 12, 2015.
79. Merck takes initiative to study cardiovascular effects of diabetes drug. NRD 2009;8:8–9.
80. Light D. Advanced Market Commitments: Current Realities and Alternate Approaches. Amsterdam, Netherlands: HAI Europe; 2009.
81. Selgelid, MJ. A full pull program for the provision of pharmaceuticals: practical issues. Public Health Ethics 2008. 1(2):133–45.
82. Mercer Management Consulting. World Bank HIV Vaccine Industry Study: Draft Summary. London, UK: Mercer Management Consulting; 1998.
83. Wilson P. Giving Developing Countries the Best Shot: An Overview of Vaccine Access and R&D. Geneva, Switzerland: Oxfam International; 2010.
84. Outterson K, Smith R. Counterfeit drugs: The good, the bad and the ugly. Alb LJ Sci Tech 2006;16:525–43.
85. International Federation of Pharmaceutical Manufacturers Associations (IFPMA). The Pharmaceutical Innovation Platform: Sustaining Better Health For Patients Worldwide. Geneva, Switzerland: International Federation of Pharmaceutical Manufacturers Associations; 2004.
86. Hubbard T, Love JA. New trade framework for global healthcare R&D. PLoS Biology 2004;2:147–50.
87. Love J, Hubbard T, Khor M, et al. Request to Evaluate Proposal for New Global Medical R&D Treaty. 2005 Feb 24.
88. Bangladesh, Barbados, Bolivia and Suriname. Proposal for WHO Discussions on a Biomedical R&D Treaty. 2009 April 15.
89. World Health Organization. WHO: WTO and the TRIPS agreement. Available at: http://www.who.int/medicines/areas/policy/wto_trips/en/. Accessed April 12, 2015.
90. European Generic Medicines Association. EGA—Data exclusivity. Available at: http://www.egagenerics.com/gen-dataex.htm. Accessed April 12, 2015.
91. So AD. A fair deal for the future: flexibilities under TRIPS. Bull World Health Org 2004;82:811–90.
92. Sukkar E. Should pharmaceuticals be allowed to transfer marketing rights for neglected diseases? Scrip World Pharmaceutical News. Available at: http://www.mmv.org/newsroom/publications/should-pharmaceuticals-be-allowed-transfer-marketing-rights-neglected-diseases. Accessed April 12, 2015.
93. Towse A. Final Report for the WHO Commission on Intellectual Property Rights, Innovation and Public Health: A Review of IP and Non-IP Incentives for R&D for Diseases of Poverty. What Type of Innovation is Required and How Can We Incentivise the Private Sector to Deliver It?. London, UK: OHE Consulting; 2005.
94. World Health Organization. WHO Expert Working Group on R&D Financing. Coordinating arrangements for R&D. 2009.
95. Knowledge Ecology International. Comments of Knowledge Ecology International (KEI) to the WHO public hearing for Proposals for new and innovative sources of funding to stimulate R&D. 2009 April 15.
96. Medical Research and Development Treaty (MRDT). Discussion Draft 4. 2005 Feb 7.
97. Conceição P. Financing for Health R&D that Addresses Challenges of the Poor: Context, Analytical Framework, and Initial Compilation of Options [Draft]. 2009 Nov.
98. DiMasi JA, & Grabowski HG. Patents and R&D Incentives: Comments on the Hubbard and Love Trade Framework for Financing Pharmaceutical R&D. 2004 June 25.
99. Integrated Regional Information Networks. In-depth: 'Lazarus Drug': ARVs in the Treatment Era. Johannesberg, South Africa: Integrated Regional Information Networks; 2005.
100. Sanjuan JR. U.S and E.U Protection of pharmaceutical test data. Consumer Project on Technology. Available at: http://www.cptech.org/publications/CPTechDPNo1TestData.pdf. Accessed April 12, 2015.
101. Chaudhuri S. TRIPS and Changes in Pharmaceutical Patent Regime in India. Joka, Calcutta: Indian Institute of Management Calcutta; 2005.
102. Health Action International Global. Response to the Expert Working Group on Alternative Financing. 2009 April 15.
103. Farlow A. A global medical research and development treaty: sn answer to global health needs? Available at: http://www.who.int/phi/ewg3rdmeet/en/index.html. Accessed April 12, 2015.
104. World Health Organization. Public health: innovation and intellectual property rights. Available at: http://www.who.int/intellectualproperty/documents/thereport/ENPublicHealthReport.pdf; 2006. Accessed April 12, 2015.