

## **ACHIEVING BOTH ACCESS AND RESEARCH:**

### **A SECTOR AGREEMENT IN PHARMACEUTICALS**

This paper explores mechanism for achieving both global drug access and research. It considers four decisions that must be made: encouragement of research, access for the poorest, treatment of the pharmaceutical industry, and treatment of middle-income countries. It then presents a plausible international agreement based on the decisions.

#### **Encouraging research on new drugs of importance to developing countries**

At one time, it seemed possible that there would be two ways to develop new drugs and vaccines that are needed for the developing world and lack any substantial market in the developed world. One track would be based on incentives for the private sector to invest, e.g. tax incentives, special exclusivity in the developed world in return for developing a new drug for the developing world, or an advance purchase commitment. The second track would be based on “public-private partnerships” (PPPs) in which, typically, foundation funding supports a non-profit virtual drug development entity that works together with public and private laboratories and research groups to attempt to bring new drugs to market. As it turns out, the PPPs have been working closely with private industry, and the two tracks have essentially merged.<sup>1</sup>

For global equity, it is essential that these “international orphan drugs” be developed and used. It is also equitable that the developed world taxpayer bear these research costs. The normal and obvious purchasers for such drugs are the global donors, working through such organizations as the Global Fund for AIDS, TB, and Malaria (GFATM) and the Presidents Emergency Program for AIDS Relief Fund (PEPFAR). These entities now buy a significant share of the drugs -- according to WHO 2000 data, (developing world) public sector purchases of drugs in the poorest nations were about \$ 3 B, and private sector purchases about \$ 7.6 B.<sup>2</sup> Since then, the global programs have been created, with PEPFAR currently spending about \$0.8 B annually on drugs<sup>3</sup> and the GFATM spending about \$ 0.9 B.<sup>4</sup> Although these institutions do not yet make up the majority of the expenditures of the poorest nations, they are likely to be the primary buyers for new drugs, especially those for needs specific to developing nations.

Can these purchasers, along with groups such as the Bill and Melinda Gates Foundation, provide adequate incentive for the development of important new drugs. Why not? Their analogues – the public health systems in developed nations (strengthened, admittedly, by the U.S. private sector), have provided adequate incentive to development of drugs for developed nation needs. These global entities will have the incentive to make solid judgments as to the balance between product quality and price – and their purchasing will be made with much greater flexibility than is available with any form of advance purchase commitment or prize. It is possible, for example, that new preventive vaccines, particularly for HIV, might ultimately be cost-effective in comparison with current therapeutic medicine, but this is not necessarily the case, and the world deserves the flexibility to buy the vaccine or the therapeutic according to the economics of the time and the product. It is reasonable to expect entities – whether profit-making or PPP -- who invest in research for these orphan drug products to bear the scientific risks that their

products will not work and the medical risks that they will not serve a market need; it is not reasonable to expect them to bear the political risks that no funds will be available. This payment requirement amounts to a version of the advance purchase commitment, only it would be made by the global funds and foundations in their normal course of business – and, like almost any other approach ultimately be borne in large part by the taxpayers of the developed world, and also likely to bring benefits for the firms of that world.

To make this form of commitment credible, the global funds need strengthening in two ways. First, they need to promise to pay a price that covers research when a product is designed specifically for the developing world. A logical approach is an estimate of the social benefit of the product to be paid for a period comparable to the effective patent term in the pharmaceutical industry. Defining “social benefit” is not easy – but it should be made by a comparison of the benefits of the new drug and the medical status before the drug. It is also important to carry out the calculations with a reasonable number for the value of a “quality adjusted life year,” (QALY). This measure may seem likely to lead to a high price – but the price should be high enough to encourage research, and this area is where research is probably most beneficial to society. There should, of course, be adjustments for the extent to which the research costs on these products have been covered by front-end foundation or public-sector support or by markets in the developed world. (It is also reasonable for developed-world purchasers to pay a share of the research costs for such drugs when they are procured for travelers and for the military, in order to take into account the fact that the benefits to this small market reflect only a portion of the social value of such drugs.) Second, it is essential that the global funds be adequately financed. Hence, an important part of the overall package must be a donor-nation commitment that the global funds will be maintained at a particular level, at least for those areas where product development is especially to be encouraged. Donors will be unwilling to offer an open-ended commitment; they may be willing to offer a fixed level for a long period or a level indexed to a measure of health need in the poorest nations, and they may be willing to extend the offer to partial coverage of the needs of the poorest in middle-income nations.

### **Access to low cost drugs for the poorest**

For drugs developed for developing-nation needs, so that research costs can be recovered in the developed world, it is appropriate that there be a generic market with low prices for the donor funds and the public and private sectors in the poorest nations. This is both a matter of equity and a matter of sustainability of the donor-nation commitment. The generic market would be like the pre-TRIPS generic market once available to developing nations that had no pharmaceutical patent. It would also be like the developed world’s post-patent generic market – but would come before patent expiration in the developed world. It could be achieved by differential pricing by the pharmaceutical producers as well as by the entry of generic firms. This pattern will apply to an increasing portion of drugs, since the disease patterns of the developed and developing world are converging.

The net cost to the poor and to the global funds (who will, in large part, be developed world taxpayers and foundations) when they are buying these pre-developed drugs is thus kept as low as possible through procurements of these drugs at generic price levels. The arrangement, of course, requires solid mechanisms to assist in restricting flow of the low-cost generic products back to developed-world markets, until the drugs go off patent in the developed world.

This generic market may require some encouragement. The TRIPS-Doha arrangements to allow generics in low income nations have been only somewhat successful. Thus, the number of HIV patients requiring anti-retrovirals in Africa is reported to be approximately 4.7 million, with only 810,000 receiving such treatment.<sup>5</sup> Generics are apparently contributing some 65 % of this market.<sup>6</sup> This is enough to help, but nowhere near the need, and the sources are probably the traditional Indian and South African suppliers. The TRIPS/Doha mechanisms have not brought new suppliers, save for Apotex's entry in 2007. The success of Indian exporters may well have depended in part on the availability of an Indian market to cover start-up and fixed costs, which are certainly not as high as research costs, but are nevertheless significant. Hopefully, the availability of the global fund market (and the ability of the funds to offer prices that cover start-up costs if necessary) can assist in building a strong generic market. There has been successful experience in the vaccine sector where the buying policies of UNICEF (which reach about 40 % of the world's childhood vaccines) have led to a new generation of Indian developing-world vaccine manufacturers, making that nation the world's second largest supplier.<sup>7</sup>

A particularly useful form of encouragement can be provided by the poorest nations themselves. The drugs currently available in these nations are often terrible – it is common that as many as 15 % of the available pharmaceuticals are bogus, and in some cases 50 %.<sup>8</sup> And actual prices faced by developing world patients are often far higher than world market prices.<sup>9</sup> In order to make the generic market effective, it is therefore reasonable for all nations receiving the benefit of the low prices to deal with these problems and to make their markets as open and transparent as possible. This would assist in building a generic market large enough to attract the substantial investments that are needed in a sector with substantial economies of scale. It would ideally include elimination of all tariff, tax, and, to the extent possible, regulatory barriers. The most difficult issues here are product safety and quality review. There is really no reason for every nation to organize its own product safety review. It is expensive, it may become a basis for corruption, and it slows product entry. It would be best to carry out regulatory harmonization absolutely globally, but the current effort being pursued at the International Conference on Harmonization, is a long way from success. A reasonable approach would be for all nations benefiting from the new generic drug market to accept a review process that could be defined by the WHO, might depend on the existing leading regulatory agencies, and could provide for special exceptions where a nation has a specific concern. And, all nations, should commit themselves to deal with the problems of counterfeit drugs and corruption in distribution chains – this may, of course, be sometimes much more a matter of obtaining technical assistance than of adopting new laws.

### **The developed world pharmaceutical industry**

At the global level, it is desirable to seek a balance that will make the research-based pharmaceutical an ally of reform rather than an opponent. This makes negotiations more feasible, and it builds toward the ideal time when all members of the world community will be able to pay a share of drug research costs and the industry will research drugs that bring the greatest social benefit. Such a balance was found in the win-win compromise that resolved a similar U.S. pharmaceutical problem: the compromise of the 1984 Hatch-Waxman Act.<sup>10</sup> One side of this compromise gave the research-based industry the benefits of patent term extension to allow for a portion of the patent term lost during the drug registration process. The other side created the vibrant U.S. generic drug industry that has contributed to lower prices upon

termination of patents. This was done by allowing the U.S. Food and Drug Agency (FDA) to approve a generic drug upon showing that the drug was biologically equivalent to an existing drug that had had the benefit of clinical trials and was going off patent. The Act included several provisions designed to facilitate generic entry that have since given rise to bizarre licensing agreements and serious antitrust concerns.<sup>11</sup> But these provisions were not central to the basic concept of the legislation, nor to its benefits, which included the growth of the generic industry from 19 % (by unit) of the U.S. market in 1984 to 42-43 % after 1995.<sup>12</sup>

Although there are other possible options for gaining pharmaceutical industry support, the most reasonable is probably a commitment that developed-world public health agencies will all pay a reasonable share of research costs. The U.S. market is particularly significant for the industry and for this trend. The United States made up 52.9 % of the world pharmaceutical market (by value) for pharmaceuticals in 2000, up from 18.4 % in 1976,<sup>13</sup> and it is, in large part, the market in which pharmaceutical firms expect to recover their research costs. Yet, it seems clear that political pressures within the United States will, sooner rather than later, lead to political action changing the health care system, and ultimately to price controls on pharmaceuticals. Unless the price controls are applied thoughtfully, the result will be to decrease incentives for research. Such harm may already have occurred in the U.S. childhood vaccine industry.<sup>14</sup>

How precisely to define the needed government commitments to protect the possibility of recovering research costs is a matter for discussion. The task is defining commitments that can give industry enough confidence to invest and that, at the same time, remain acceptable to taxpayers. And, ideally the commitments should be economically rational. An excellent approach is laid out in the recent UK Office of Fair Trading market study on that government's pharmaceutical purchases.<sup>15</sup> It calls for a "value-based approach to pricing, which would ensure that the price of drugs reflect their clinical and therapeutic value to patients and the broader National Health Service." Such an arrangement is fair to both the pharmaceutical industry and the taxpayer who is supporting the National Health Service.

Value-based pricing requires that the price be low enough that the drug is cost-effective. As noted above, the cost effectiveness analysis depends on a number of assumptions. Crucially, it compares the costs and benefits of a drug against an alternative treatment, which may be another drug. Given that there may be several drugs applicable to a particular indication, it is wise not to base the cost-effectiveness on currently competing drugs, but to choose, perhaps, the treatment prevalent some years (seven?) before the new drug comes on the market, and then to apply the minimum price during the patent period. Again, it is important to do the calculations with an appropriate number for the value of a QALY.

This approach amounts to a commitment to the current patent-based pharmaceutical development model. Admittedly, that model is under pressure, most importantly with respect to the declining pace of new drug development.<sup>16</sup> It is certainly possible to consider other models of pharmaceutical development, such as models based on direct government support of research as in the defense sector. Yet, such approaches are very subject to political fads – there is benefit in an endogenously determined research level with decentralized decision-making (rather than a research level set by explicit political decision), and in the pharmaceutical sector there can always be a mix of private and public support of research oriented toward particular needs.

## **Middle-income nations**

In designing any drug development and access proposal, an important group of issues arises in the middle income nations. This is where patent battles are currently being fought most fiercely, because these nations have the markets that are likely to show the greatest growth over the next decades as real incomes and purchasing power rise. The pharmaceutical industry correctly sees these areas as its future market. And it is middle income nations such as Colombia and Thailand that are receiving especially strong U.S. pressure to strengthen intellectual property protection.

At the same time, in nations such as Brazil and Thailand, there are programs for national production of drugs through compulsory licenses of products still on patent. And many middle-income nations include many very poor people – there are more people living in absolute poverty in South Asia than in Africa.<sup>17</sup> Moreover, inclusion of some of these markets in a world generic market may assist in making a generic market economically feasible for the poorest.

It is clearly essential therefore to define a special set of rules for the middle-income tier. As they reach some income level, these nations must be treated as developed nations and must pay their full share of research costs. Moreover, they will, at some point of development, face pressure from their own industries for stronger patent protection. But in the short run, it might be possible to allow the public sector (or, if the market could be so divided, the poorest in these nations) to have access to the developing-world generic market, while the private sector market would be subject to patents under developed-world standards. It is of course difficult to separate markets within a nation, and there are serious risks of corruption in such an effort. Another approach might be to have a reduced patent term for pharmaceuticals for these nations, so that the post-patent generic market would become available sooner than in the high-income nations.

## **Putting it all together**

It is hard to see how these ideas can be implemented without dealing with TRIPS issues – after all, the current special arrangements for the developing nations will expire in 2016 – a time within the current planning horizons for pharmaceutical research programs. Why not make the key agreement a sector-specific code within the WTO? There have already been WTO sector-specific arrangements for agriculture and aircraft, as well as proposals for such arrangements for steel. Drug-pricing provisions have been included in the 2004 U.S.-Australia Free Trade Agreement. And a WTO code would also provide the assurance that a nation's failure to live up to its commitment could be brought before a WTO Panel, and thus provide some basis to enforce the national commitments to continue funding global drug access programs and to pay appropriate prices for pharmaceuticals. The following is a plausible package -- and there might reasonably be time limits on certain of the provisions:

- (1) Developed-world nations would commit themselves to develop detailed mechanisms to ensure that their government pharmaceutical purchasing authorities pay at least a price that reflected the clinical value of drugs, as measured by their own health needs, and that they pay a price adequate to cover an appropriate share of research costs for their

purchases of new products of primary value to developing nations.

- (2) Low-income developing nations, as well as global funds such as GFATM and PEPFAR and relevant foundations, would be permitted to purchase generic versions of all drugs including those on patent, except that the global funds would pay prices that cover an appropriate share of research costs for new products whose primary value is in developing nations.
- (3) Middle-income nations would divide their market with the public sector benefiting from the generic price and the private sector paying the developed-world price.
- (4) All nations would prohibit the trade in counterfeit drugs, would cooperate with generic and research pharmaceutical firms to help suppress it, and would assist in preventing the reverse flow of low-income-nation generic drugs to high-income nations.
- (5) All beneficiaries of the new form of generic pricing would remove all legal tax, duty, and similar barriers to the import and marketing of pharmaceuticals. They would further agree to accept new drugs on the approval of those drugs by a new process to be set up by WHO.
- (6) Donor nations would commit themselves to support the global funds at a defined level.
- (7) The various national commitments to use such arrangements would be enshrined in an international agreement in the WTO, implemented in national legislation.

Each of the components is economically defensible. And the likely perceived political costs and benefits are reasonably balanced for each community and among the different communities.

## Endnotes

- <sup>1</sup> See Mary Moran et al, *The new landscape of neglected disease drug development*, (London School of Economics and Wellcome Trust, Sept 2005).
- <sup>2</sup> World Health Organization, *The World Medicines Situation* (2004).
- <sup>3</sup> Calculated from PEPFAR website.
- <sup>4</sup> Calculated from overall funding levels from GFATM website and observation by J. Quick that about 40 % of the expenditures are expected to go for drugs, J. Quick, Ensuring access to essential medicines in the developing countries: A framework for action. *Clinical Pharmacology & Therapeutics* 73: 279-283 (2003).
- <sup>5</sup> World Health Organization, *Progress on Global Access to Antiretroviral Therapy: A Report on "3 X 5" and Beyond* (March 2006).
- <sup>6</sup> C. Chien, HIV/AIDS Drugs for Sub-Saharan Africa: How Do Brand and Generic Supply Compare? *PLoS ONE* 2(3): e278 (March 14, 2007).
- <sup>7</sup> See J. Barton., A History of Developing World Production of Vaccines and Access to Vaccine Technology, forthcoming, *Economic Development and Cultural Change*.
- <sup>8</sup> Calculated from *World Medicines Situation*, supra.
- <sup>9</sup> T. Richards, The great medicines scandal, *BMJ* 332 1345-1346 (10 June 2006). The underlying study is World Health Organization and Health Action International, *Price, availability and affordability; An international comparison of chronic disease medicines*, WHO-EM/ED8/068/E (2006).
- <sup>10</sup> Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417.
- <sup>11</sup> See, e.g. U.S. Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration; An FTC Study* (July, 2002).
- <sup>12</sup> E. Berndt, Pharmaceuticals in U.S. Health Care: Determinants of Quantity and Price, *Journal of Economic Perspectives* 16 (4) 45-66 (2002).
- <sup>13</sup> *World Medicines Situation*, supra.
- <sup>14</sup> Institute of Medicine, *Financing Vaccines in the 21<sup>st</sup> Century: Assuring Access and Availability* (2004).
- <sup>15</sup> UK Office of Fair Trading, *The Pharmaceutical Price Regulation Scheme* (February 2007).
- <sup>16</sup> See J. Barton & E. Emanuel, The Patents-based Pharmaceutical Development Process, *JAMA* 294: 2075-2082 (2005). S. Chan & M. Ravallion, *How have the world's poorest fared since the early 1980s?*, (World Bank, Fall 2004).
- <sup>17</sup> S. Chan & M. Ravallion, *How have the world's poorest fared since the early 1980s?*, (World Bank, Fall 2004).