

## Viewpoint

## Out-licensing: a practical approach for improvement of access to medicines in poor countries

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There is much disagreement between the pharmaceutical industry and advocacy groups about how to provide patented medicines in poor countries. While everyone agrees that access to medicines in developing countries should be improved, too often this shared sensibility is submerged by an excess of timid incrementalism by industry, and demagoguery by activists. Neither contribution is constructive, as evidenced by the rancour of the debate (with phrases such as “murder by patent”), which has distracted everyone from the only focus that matters from a humanitarian perspective—the urgent needs of the patients.

Here, we propose a practical, consensus approach, which we advocate as authors based in a brand-name pharmaceutical company (MAF), a non-profit generics company (HdB), and public health and legal academia (AA).

Specifically, we propose that, in appropriate instances, pharmaceutical patent holders should award out-licences (or voluntary licences) to generic manufacturers who agree to manufacture and supply medicines to poor, developing countries. Under the legally binding terms of these licence agreements, several generic manufacturers could compete against one another on price in poor countries, but would not be allowed to compete against the patent holder in rich countries, where revenues and the incentives for inventing new medicines would be undiminished. Use of out-licensing in this way separates these fundamentally different markets, promoting access to affordable medicines for the world’s poor, while reaffirming patents as indispensable for successful pharmaceutical research.

### Why out-licensing?

Contrary to conventional wisdom, pharmaceutical patents only rarely impede access to medicines in poor countries. Most pharmaceutical companies infrequently seek patents in poverty-stricken countries, because to do so is rarely profitable.<sup>2</sup> Thus, to allege that “patents [are] . . . a barrier in many places to accessing affordable medicines”<sup>3</sup> overstates the case.

Nevertheless, the fact that patents could impede treatment access in developing nations, if only sometimes, is sufficient reason to resolve that problem. Doing so need not financially damage pharmaceutical companies, since

Africa, the Indian subcontinent, and the poorer countries of Asia total only 1·2%, 1·3%, and 2·6% of the global pharmaceutical market, respectively, and the proportions are even smaller for the sales of patented medicines (calculations based on data from <http://www.imshealth.com>). Accordingly, most companies agree that provision of certain patented medicines at a discount or for free in poor countries is a humanitarian imperative, the value of which exceeds the minor revenues that are forfeited.

However, these donations or discounts offer only limited, often imperfect, solutions. Donation programmes are only suitable for the few medicines that are highly effective with short treatment courses. This fact explains why several companies (Merck, Pfizer, GlaxoSmithKline) can donate antihelmintics or antibiotics with infrequent treatment protocols—eg, once yearly—but no company can widely donate antiretroviral therapies for HIV/AIDS, which need to be taken daily and for life. In such instances, companies might instead discount the products to what they consider a fair or equitable price, but this can create great acrimony. The experience of GlaxoSmithKline is cautionary: although the company was the first to discount its HIV/AIDS medicines in poor countries, and did so repeatedly, activists still considered its prices excessive, leading Oxfam to scorn the effort, and other non-governmental organisations to bring suit. Much energy and goodwill was lost, without helping patients.

Another risk is that discounted or donated medicines intended for poor countries could be diverted, and damage pharmaceutical markets in rich countries. The law currently lacks adequate safeguards against these products being reimported by profiteers and sold in rich countries, and might even unhelpfully resort to reference pricing,<sup>4</sup> which pegs prices in rich countries to the lowest world price. Either action could ultimately destroy a company’s ability to sustain pharmaceutical discounts or donations. This danger is not merely theoretical: in 2002, Belgian authorities discovered that one third of the discounted HIV/AIDS drugs GlaxoSmithKline provided to Africa were diverted and sold in Europe, robbing thousands of African patients of medicines.<sup>5</sup>

Out-licensing avoids all these difficulties. By ceding the poor countries to generic manufacturers, the patent holder enables competition there and avoids acrimony over its pricing. The lower generic prices would not spread to the rich, developed countries, because reference pricing laws do not treat generics as comparators. Similarly, the generic goods would not reach the rich countries, as is proved daily by the fact that the many foreign generic drugs do not flood and destroy these markets, even for the costliest medicines. Thus the scheme is inherently more secure, and could be further bolstered by penalties in the licence agreement.

These ideas are not original. GlaxoSmithKline, Boehringer Ingelheim, and Bristol-Myers Squibb have experimented with limited out-licensing or waiving patent

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enforcement in South Africa. Numerous international commissions,<sup>6</sup> United Nations agencies,<sup>7</sup> African governments,<sup>8</sup> generics firms,<sup>9</sup> and campaigning non-governmental organisations<sup>10-15</sup> have advocated out-licensing, often as an alternative to compulsory licensing—ie, patent expropriation. Groups such as the Treatment Action Campaign and Médecins Sans Frontières have challenged “pharmaceutical companies . . . to offer non-exclusive voluntary licenses”, while signalling that progress of this kind would “eliminate the unnecessary conflict between activist[s] . . . and drug companies”.<sup>16,17</sup>

By making wider and broader use of out-licensing than at present, pharmaceutical companies can satisfy these many expectations, and enhance—not ruin—their standing in public opinion and the capital markets. Although companies might not grant every request for an out-licence, every request deserves systematic consideration, with more seriousness and sympathy than hitherto evident.

### How to out-license

Use of out-licensing to improve access of medicines in poor countries need be no more difficult than out-licensing for routine business purposes. Any pharmaceutical company that does the latter—ie, virtually all of them—should consider the former, based on six principal issues.

#### *Which product?*

A company can out-license any product that it alone has patented, or for which it has obtained full rights under assignable in-licence(s) from the original patent holder(s). However, if the company’s rights are not full, or derive from non-assignable in-licence(s), then the consent of all other legal owners is needed, or no out-licence can be granted.

Legally, out-licensing is only relevant for medicines under patent in a developing country, and it is unnecessary where patents do not exist or have expired. Medically, the greatest benefit will be for those medicines that treat the leading causes of infectious and non-infectious mortality and morbidity in developing countries.<sup>18</sup> The *WHO Model List of Essential Medicines*<sup>19</sup> lists the most cost-effective and practical medicines for these major diseases, including about 20 that are patented in developing countries. All of these medicines are excellent candidates for out-licensing, though others could be as well.

#### *Which licensees?*

Because the point of out-licensing is to strengthen price competition in poor countries, non-exclusive licences are preferable to exclusive ones, with no specific ceiling on the number of generic manufacturers who obtain licences. An exception might apply for products with unusually small sales volumes; in which case, capping the number of licences or the price that licensees may charge can facilitate access without diluting the financial incentives too greatly.

Generic licensees need not necessarily be located in the developing countries where they are authorised to sell their products. One could license a generic manufacturer in Canada, for example, on the terms that it only supplies drugs to Africa, and never in North America. Obviously, competition is maximised by placing no geographical restrictions on where manufacturing is based, and this promotes the cheapest, fastest access to medicines. Insistence on local manufacturing, while advocated by some, would actually detract from this aim.

The most important feature of a licensee is proper attention to product quality, equivalent to the branded

pharmaceutical. At a minimum, licensees must obtain certification of Good Manufacturing Practice (GMP), and prove bioequivalence and batch consistency for their products. Upholding these standards requires at least two stages of quality assurance: first when the licence is applied for by established GMP manufacturers; and second when the product has been manufactured and tested for batch consistency and bioequivalency. Practically, a “licence now, certify later” policy is most expeditious, a situation in which the generic company secures a provisional licence before investing in manufacturing, on the terms that the company shall in no circumstances supply its product for medical use before the quality requirements have been satisfied, as judged by an independent third party. The International Dispensary Association, which is the world’s largest non-profit supplier of generic medicines, serves that quality assurance function for hundreds of products, although various United Nations agencies (WHO, UNICEF, UNAIDS) or government offices (FDA, EMEA) could as well.

#### *Which developing countries?*

Since the purpose of out-licensing is to draw a beneficial distinction between the world’s rich and poor medicine markets, these markets need to be defined clearly in the licence agreements themselves.

The WHO Commission on Macroeconomics and Health, which included both industry and activist representatives, identified a subset of developing countries with a per capita gross national product (GNP) of less than US\$1200 or severe epidemics—eg, greater than 1% of adults with AIDS—that are least able to afford priority health interventions, including medicines.<sup>6</sup> Application of these two criteria alone captures 78 countries (including all of sub-Saharan Africa) where 3·8 billion people live amid poverty and illness. Economic output per person is just 2% that of the average American, and life expectancy is 22 years shorter.

However, among these 78 countries are difficult cases, such as China or India, where the existence of a few elite cadres affects out-licensing schemes intended for the poor majority. Whether or not pharmaceutical companies, as outsiders, have an ethical duty to act in place of governments that do not deploy their extensive financial and industrial capacity to provide for their poorest is arguable—for instance, China and India spend relatively little on public health, and billions on nuclear weapons. Although one could theoretically structure out-licences to supply only that segment of the national market that caters for the poor, indications are that the wealthy elites could corruptly misappropriate those medicines. Some discretion is, therefore, appropriate before out-licences are used to supply countries with large internal wealth inequalities or public-health underspending, perhaps by making that privilege conditional on the government progressively increasing the health budget spent on the poorest.

Finally, the internal trade laws of the European Union make it impossible to include the European Union accession countries in out-licensing arrangements.<sup>20</sup> Once these countries join the European Union, goods become freely tradable in all the countries of the Union, affecting all Western European pharmaceutical markets and revenues.

#### *Which rate of royalty?*

The chairman of the Treatment Action Campaign has urged patent holders to “grant non-exclusive licenses in the developing world to generic producers,” as we propose, “in

exchange for a 5% royalty on their sale prices".<sup>21</sup> The basic fairness of compensation is not questioned by activists or the generics industry.<sup>9,22,23</sup>

A nominal royalty, of 5% for example, is attractively simple. However, a country's economic or epidemiological condition might merit variation above or below that number. For example, Brazil (per capita GNP US\$3600; HIV-1 infection rate 0.7%) can afford a higher royalty on an AIDS medicine than Malawi (per capita GNP US\$170; rate of HIV-1 15%). Royalties can help offset the costs of the out-licensing programme, though licensors could in some cases dedicate them to charities or research, or waive them.

#### *Which legal rights?*

To be effective, an out-licence must at the very least grant generic manufacturers the rights to manufacture, sell, and distribute a medicine in designated countries, with the last two rights being assignable to local wholesalers and retailers down the supply chain. Dependent on the characteristics of the developing country's regulatory scheme, portions of the product's dossier could be provided to assist the manufacturer—eg, for transferring proprietary manufacturing technology and safety data.

Furthermore, there could be long-term benefits to granting manufacturers the right to undertake new pharmaceutical research, which could result in beneficial spin-offs from the original medicine—eg, new formulations, or fixed dose combinations with other medicines to improve dosing convenience and therefore patients' adherence to therapy. Some of these spin-offs could even be profitable in the rich countries. By pairing the licensee's experimental rights with the quid pro quo that the licensor enjoys a right of first refusal to share or comarket those spin-offs, the arrangement is equitable for both companies.

#### *Which enforcement mechanisms?*

The greatest, long-term threat to this proposal is that generic medicines manufactured under licence could escape the developing countries where they are authorised, and leak into rich countries. Fortunately, the structure of pharmaceutical markets makes it inherently difficult (and illegal) to sell the licensee's generics in rich countries without regulatory approval. These illegal imports would also not be reimbursed under insurance or government health plans, which explains why, of the abundant generics now on the world market, hardly any reach Europe or North America illicitly.

Nevertheless, further legal safeguards should be possible. Licensees could be required to make their pills a different colour and shape from the brandname product. Licensing contracts could reverse the onus and presume a breach whenever a licensee's medicines were discovered in an unauthorised country. Contracts should also include a choice-of-jurisdiction clause, and might specify binding arbitration instead of costly litigation, with damages or revocation of the licence as penalties in especially bad cases of breach.

#### **Is this proposal practical?**

These six principal issues provide a general framework to facilitate discussions about out-licensing, while also proving that none of the legal or operational issues are unanswerable. We hope that this report cures an omission in the current dialogue, where there is widespread support for out-licensing, but little pragmatic guidance on actually doing it.

We believe that out-licensing, to improve access to medicines, should be pursued systematically. Companies

should, for instance, consider taking a few, experimental steps to offer out-licenses on the WHO Essential Medicines, and possibly others. Because each disease and medicine is different, out-licensing transactions should not be thought of as setting inflexible precedents, and each out-licence will probably need to be somewhat different from others that precede it (assuming, of course, that out-licensing is the best option for that medicine, which is not always true).

If this recommendation is acted on, a diverse number of approaches to out-licensing will soon exist. However, we note two potentially serious concerns.

First, in some cases out-licensing could actually harm developing countries, because in ceding those markets to licensees, pharmaceutical companies will necessarily reduce their local presence—including in medical education and philanthropy. The generic licensees who might supply Africa with HIV/AIDS medicines could never match the efforts of companies today: between them, Abbott, Bristol-Myers Squibb, Merck, and Pfizer have pledged US\$275 million for HIV/AIDS in developing countries, most of it in cash.<sup>24-27</sup> Philanthropy on this scale exceeds the foreign aid contributions of several G-7 countries.<sup>28</sup> Activists who demand that companies disengage from developing countries by out-licensing, perhaps for ideological reasons, also risk sacrificing this major source of AIDS funding.

Second, the success of any out-licensing experiment will hinge on economic conditions outside of the companies' control. For example, the value of out-licensing an HIV/AIDS medicine is limited by the frustrating, multibillion-dollar shortfall of foreign aid money for HIV/AIDS treatment, which left uncorrected will mean few buyers for the generic product, and thus few or no interested generic manufacturers. An out-licensing experiment would then fail—and with it, the proof of principle that might encourage other pharmaceutical companies to pursue out-licensing.

Let this example be a warning. There are efforts that research-based pharmaceutical companies can, and ethically must, make to provide medicines—such as out-licensing—but other efforts that lie beyond their competence or domain. If the efforts of companies are to succeed, they must be generously reciprocated by the rich nations as foreign aid donors, to fund not only the purchase of medicines, but other elements of public health. Neglecting these obligations in a time of great public-health crisis, as the G-7 countries are doing, is morally scandalous. By using out-licensing to answer the concern that patents impede treatment access, the onus now rests squarely on the donors to contribute their share—or to assume responsibility for the deadly, globally devastating consequences.

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#### **References**

- 1 Booker S, Minter W. Global apartheid. *The Nation*, July 9, 2001.
- 2 Attaran A, Gillespie-White L. Do patents for antiretroviral drugs constrain access to AIDS treatment in Africa? *JAMA* 2001; **286**: 1886-92.
- 3 Médecins sans Frontières, Canadian HIV/AIDS Legal Network, Oxfam Canada, Interagency Coalition on AIDS and Development, Canadian Council for International Cooperation, Canadian Treatment Action Council. An open letter to all members of parliament. October

- 25, 2001. [http://www.msf.ca/access/pics/msf\\_letter\\_par\\_e.pdf](http://www.msf.ca/access/pics/msf_letter_par_e.pdf) (accessed Oct 9, 2002).
- 4 Anon. A bill to amend the Federal Food, Drug, and Cosmetic Act to provide greater access to affordable pharmaceuticals (107th Congress), S 812, amendment 4300 (US Senate).
- 5 Boseley S, Carroll R. Profiteers resell Africa's cheap Aids drugs. *The Guardian*, Oct 4, 2002.
- 6 WHO Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. Geneva: World Health Organization, 2001. <http://www.cmhealth.org> (accessed Oct 10, 2002).
- 7 World Health Organization and World Trade Organization Secretariats. Report of the workshop on differential pricing and financing of essential drugs, 8–11 April, 2001, Høsbjør, Norway. [http://www.wto.org/english/tratop\\_e/trips\\_e/hosbjor\\_report\\_e.pdf](http://www.wto.org/english/tratop_e/trips_e/hosbjor_report_e.pdf) (accessed Oct 10, 2002).
- 8 "Africa Bloc Applies to WTO for License to Produce Cheap AIDS Drugs", *Reuters Medical News* (November 15, 2002). Available at <http://www.medscape.com/viewarticle/444656> (accessed Nov 19, 2002).
- 9 Cohen M. Company wants to copy AIDS drugs. *Associated Press Worldstream*, May 16, 2001.
- 10 Médecins Sans Frontières. From Durban to Barcelona: overcoming the treatment deficit (July 2002). <http://www.accessmed-msf.org/upload/ReportsandPublications/18720021525252/FINAL%20Policy%20Doc%20EMBARGOED.pdf> (accessed Oct 10, 2002).
- 11 Oxfam. Implausible denial: why the drug giants' arguments on patents don't stack up. <http://www.oxfam.org.uk/policy/papers/trips/trips2.htm> (accessed Oct 10, 2002).
- 12 AIDS Healthcare Foundation. US' largest AIDS organization calls Glaxo AIDS drug announcement a 'hollow gesture'. <http://www.aidshealth.org/NewsRoom/press/PR090602.htm> (accessed Oct 10, 2002).
- 13 Consumer Project on Technology, Health Action International, Médecins Sans Frontières, Oxfam and Treatment Action Group. Joint statement on the WTO/WHO on differential pricing and financing of essential drugs (April 11, 2001). <http://www.cptech.org/ip/wto/norwaystatement.html> (accessed Oct 11, 2002).
- 14 Health GAP. What is Health GAP (Global Access Project)? [http://www.globaltreatmentaccess.org/content/press\\_releases/02/070402\\_HGAP\\_PP\\_whaishgap.pdf](http://www.globaltreatmentaccess.org/content/press_releases/02/070402_HGAP_PP_whaishgap.pdf) (accessed Oct 11, 2002).
- 15 ACT UP. ACT UP demands: break the patents, treatment for all (July 11, 2000). <http://www.actupny.org/reports/durban-breakpatents.html> (accessed Oct 11, 2002).
- 16 Treatment Action Campaign. Defiance campaign: questions and answers about TAC and MSF importing generic medicines from Brazil (January 29, 2002). [http://www.tac.org.za/Q\\_A\\_ImportBrazil.htm](http://www.tac.org.za/Q_A_ImportBrazil.htm) (accessed Oct 10, 2002).
- 17 Achmat Z. Message from Zackie Achmat, Treatment Action Campaign (South Africa) to the 14th International AIDS Conference, Barcelona (July 10, 2002). [http://www.tac.org.za/Documents/Other/Message\\_from\\_Zackie\\_Achmat\\_Barcelona\\_10\\_July\\_2002.doc](http://www.tac.org.za/Documents/Other/Message_from_Zackie_Achmat_Barcelona_10_July_2002.doc) (accessed Oct 10, 2002).
- 18 Murray CJL, Lopez AD, eds. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge: Harvard University Press, 1996.
- 19 WHO. The selection and use of essential medicines: report of the WHO Expert Committee. WHO technical report series. Geneva: World Health Organization, 2002. [http://www.who.int/medicines/organization/par/edl/\\_Toc8099672](http://www.who.int/medicines/organization/par/edl/_Toc8099672) (accessed Dec 24, 2002).
- 20 Anon. Treaty establishing the European Community, as amended, Article 85.
- 21 Achmat Z. How to beat the epidemic. *The Guardian*, Dec 1, 2001.
- 22 Pearl D. Companies weigh offer of royalties for AIDS drugs aimed at Africa. *Wall Street Journal*, Feb 16, 2001.
- 23 Baker BK. TRIPS reform: voluntary licenses, compulsory licenses, and parallel importation (May 25, 2001). <http://www.cptech.org/ip/health/cl/bakerreport05252001.html> (accessed Oct 11, 2002).
- 24 Waldholz M. Abbott Labs improves its effort to combat AIDS in Africa. *Wall Street Journal*, June 27, 2002.
- 25 Bristol-Myers Squibb. Bristol-Myers Squibb announces accelerated program to fight HIV/AIDS in Africa (March 14, 2001). <http://www.securethefuture.com/program/data/031401.html> (accessed Oct 10, 2002).
- 26 Merck. HIV/AIDS in developing world: the Merck commitment (Dec 2, 2000).
- 27 Pfizer. Alliance to build first large-scale AIDS medical training facility in Africa. [http://www.viewsmakingnews.com/PDFs/alliance\\_to\\_build.pdf](http://www.viewsmakingnews.com/PDFs/alliance_to_build.pdf) (accessed Oct 11, 2002).
- 28 UNAIDS. Report on the state of HIV/AIDS financing. Programme Coordinating Board, 12th meeting, Geneva, May 28, 2002.