

## UNIVERSITIES ALLIED FOR ESSENTIAL MEDICINES

*Response to Key Issues Raised at 22 March Breakfast Meeting*

---

### **Key points of agreement from the 22 March meeting:**

- Penn can take steps to promote neglected-disease research including (a) lowering barriers to accepting funding from foundations and (b) creatively engaging with public-private partnerships conducting neglected-disease drug development.
- Any solutions to the access and research gaps must involve industry partners and must be implemented in a way that preserves and strengthens relationships rather than endangering them.
- A stronger commitment to solving global health problems is a way to actualize the values laid out in the Penn Compact.
- There is an opportunity for Penn to demonstrate true leadership and vision by addressing the access-to-medicines crisis.

### **How important is university licensing in limiting access to medicines in poor countries?**

*Historical data suggests that changing university licensing practices presents a non-trivial and actionable opportunity to lower prices and thereby improve access to medicines in developing countries.*

- The ownership position of universities in pharmaceutical technologies is both substantial and increasing.<sup>1</sup> Both the number of patents and, concomitantly, the number of license agreements executed by universities have approximately doubled between 1993 and 2003.<sup>2</sup> A major share of this university intellectual property is in the biomedical field.<sup>3</sup> For example, universities own patent rights in key pharmaceuticals used in recent years, including the cancer drugs cisplatin and carboplatin,<sup>4</sup> pemetrexed (Alimta),<sup>5</sup> cetuximab (Erbitux),<sup>6</sup> the anemia treatment epoetin alfa (Epogen);<sup>7</sup> the AIDS drugs stavudine (Zerit),<sup>8</sup> lamivudine (Epivir),<sup>9</sup> abacavir (Ziagen),<sup>10</sup> emtricitabine (Emtriva),<sup>11</sup> and T20 (Fuzeon);<sup>12</sup> and the best-selling glaucoma medicine latanoprost (Xalatan).<sup>13</sup>
- The case of antiretrovirals for HIV treatment shows the impact that changing licensing practices could have on prices. Stavudine (from Yale), lamivudine (from Emory), and abacavir (from U. Minnesota) were part of the World Health Organization's original recommendations for first-line therapy.<sup>14</sup> Substantial negotiations and public pressure were needed to decrease prices for antiretrovirals (in some cases from over \$10,000 per patient-year to \$120 per patient-year).<sup>15</sup> Had access-minded licensing provisions been in place *ex ante*, these difficulties would have been avoided and an untold number of lives could have been saved.
- It is difficult to appraise the precise impact of a university licensing intervention in improving access. Essentially, this is a problem of measuring missed opportunities. While one might argue that it is difficult to point to cases where university licensing was the limiting factor in expanding access, this misses the crux of why licensing is important. University licensing presents an opportunity for increasing access. This opportunity arises because universities lie far upstream in the drug development process and because universities respond to a different set of incentives than companies.
- The critical moment for taking advantage of such an opportunity has not passed. While case-by-case negotiations (e.g., Medecins Sans Frontieres and Yale with stavudine and the Clinton Foundation with a number of other antiretrovirals) have brought down the prices for first-line

HIV treatment, the underlying problem was not resolved. For this reason, we are seeing a ‘second-line crisis’ in the price of next-generation antiretrovirals that overcome growing resistance profiles and have lower toxicity than first-line drugs.<sup>16</sup> These second-line medicines will soon become mainstays of antiretroviral therapy—for example, Emory’s emtricitabine will be recommended as a first-line therapy in the latest WHO revision of treatment guidelines.<sup>17</sup>

- The view that university licensing is only important for tropical and other infectious diseases does not acknowledge the potential for helping curb morbidity and mortality caused by noncommunicable diseases in developing countries. Chronic conditions, not just infectious diseases like HIV, afflict the developing world as well. In fact, as highlighted in a recent series in *The Lancet* entitled “The neglected epidemic of chronic disease,” of the 35 million deaths that will occur in 2005 from chronic diseases, 80% of them will take place in low- and middle-income countries.<sup>18</sup>
- Perhaps the strongest argument in favor of university licensing as a means to improve access to medicines was voiced during the breakfast meeting last Wednesday: changing university licensing practices is something tangible and something that universities can do relatively easily if there is the volition to do so.

### **How could the problem of potential diversion of drugs (from developing countries to developed ones) be addressed?**

*Diversion of generic drugs has rarely been observed historically. Were it to present a greater problem, steps can be taken to ensure this diversion does not undermine pharmaceutical markets in high-income countries.*

- Diversion from poor countries is rarely observed. Generic drugs have been produced in India for decades without apparently infiltrating or undermining Western markets.<sup>19</sup> Meanwhile, the only significant media reports of diversion have been shown to be overblown. GlaxoSmithKline charged in 2002 that 36,000 packages of HIV medicines worth approximately \$18 million were found to have been diverted from a charitable initiative in West Africa to the EU.<sup>20</sup> It turned out that 99% of the packages handled by the parallel trader were not part of Glaxo’s charitable access initiative but rather ordinary commercial sales at prices approximating EU prices. Also, Glaxo did not label the packages as ineligible for sale or re-importation in the EU.<sup>21</sup>
- Insofar as diversion is a concern, it can be addressed in the same manner that the WTO has—by requiring use of different packaging, pill color, and pill shape in different countries to facilitate the identification of illegal imports.<sup>22</sup>
- The equitable access approach actually reduces the risk that medicines would be diverted to markets in high-income countries compared to a drug-donation or voluntary differential pricing approach. Differentially-priced products sold by the original, branded company (as in Canada) may be susceptible to parallel trade, particularly if they are similar in appearance. Regulatory barriers exist to prevent these medicines from entering high-income markets easily, though they are sometimes not enforced.<sup>23</sup> Generic versions of the same medicines have to overcome a second legal barrier (due to patent protection) governed by customs procedures. Moreover, consumer demand for these generics is likely to be low compared to re-imported branded products.

### **What would be the economic impact of equitable access licensing on Penn?**

*If carefully developed, we believe that access-minded licenses need not jeopardize Penn's strong relationships with the private sector or its own financial bottom line.*

- There are reasons to believe the economic impact to the pharmaceutical industry would be minimal. Low- and middle-income countries currently represent only five to seven percent of pharmaceutical industry revenue,<sup>24</sup> so the markets directly affected by equitable access licensing are small.
- In addition, impact to Penn's bottom line is likely to be small. In order to more precisely estimate the impact of the EAL at Penn, our Wharton colleagues have constructed a conservative financial model that yields possible yearly financial losses incurred due to excluding low- and middle-income (LMI) country markets from possible revenues. Preliminary data using conservative assumptions suggest that the impact on Penn's licensing revenue would be minor. We hope to improve this model in collaboration with the CTT and Penn's world-renowned health economics experts to better predict the economic impact.
- Any small revenue losses could be offset by growth of global health grant awards. An access-minded licensing policy could help attract new funding through the rapidly expanding field of nontraditional partners such as the Gates and Rockefeller Foundations. Their interest would likely be heightened by Penn's elevated status as a leader in global health.

### **Would equitable access licensing be a nonstarter in contract negotiations?**

*If we can directly address pharmaceutical company CEOs and scientific directors, highlighting the importance of access to improving global health and our estimates of potential economic impact of these policies, we do not believe that licensing provisions would block contract negotiations.*

- Pharmaceutical company leadership could be persuaded by global health concerns and public-relations benefits. It may well be that industry contract negotiators will reflexively resist equitable access licensing provisions at first. But, as Dr. Gaulton pointed out, the lawyers are not necessarily the most appropriate representatives of pharmaceutical companies' priorities. Top scientists and CEOs may be more likely to value advancement of global health, especially considering the interest in repairing the industry's public image. Penn has superb relationships with industry leaders and is well-suited to start this dialogue.
- Collective action of universities will help advance discussions with industry. The ultimate goal is for all universities involved in biomedical research to collectively adopt access-minded licensing practices, thereby maximizing impact and bargaining power with industry partners. This will only happen because of the strong leadership of major, globally engaged universities. In addition to leading the way through its own policies, specific venues where Penn could promote collective university action include the upcoming meeting of senior research officers mentioned by Dr. Molinoff and the Association of University Technology Managers (AUTM). This movement is already occurring to some extent, and as Prof. Ruger pointed out at the meeting, it is to Penn's advantage to be out in front of the pack.

## **What about access problems for the poor in the U.S.?**

*The poorest citizens in the U.S. do lack access to medicines, but government action is more likely to provide a solution than university licensing practices.*

- An access gap clearly exists within the U.S. and equitable access licensing would not provide a domestic solution. Equitable access licensing and similar mechanisms rely on the ability to divide markets into two groups—those with branded-drug exclusivity and those with generic competition. In order to apply these strategies within the U.S., we would need to believe that we could neatly divide poor and rich markets. As we all know, this would be nearly impossible. Of course we hope that the access gap will be closed in the U.S. However, government action is more likely to provide solutions to this problem than universities.
- Though licensing provisions are unlikely to provide a solution to the access gap in the U.S., the EAL should not present a PR liability for the pharmaceuticals industry. Will the public criticize pharmaceutical companies for "worrying about people abroad when there are people suffering right here"? This is a concern for any differential pricing mechanism. However, we believe that the specific mechanism of the EAL, generic competition, would offer some PR protection. After all, it would be generics manufacturers, not brand-name companies, selling at low prices. While lower prices for identical branded drugs invite public criticism, generic products do not.

## **Should middle-income countries like China be included as beneficiaries in an access-minded licensing approach?**

*Any workable system of differential pricing will have to demarcate categories. Including middle-income countries in equitable access licensing makes sense from the viewpoint of disease burden and of ensuring a viable market for generic companies.*

- The selection of territories for market segmentation will, at some point, be an arbitrary one. The theoretical optimum would be Ramsey pricing such that all prices are set on an individual basis according to relative income. This is clearly infeasible, but highlights the fact that any workable system of differential pricing will have to choose some parameters to demarcate categories.
- The only feasible way of demarcating categories is by country because of irreducible legal and regulatory frameworks in place within countries. A category of developing countries could be used to establish a market where true generic competition would reduce prices. We believe the most sensible category would include all low- and middle-income countries as defined by the World Bank.<sup>25</sup>
- Excluding middle-income countries would lessen the potential impact of the EAL on the access gap. Those middle-income countries that do grow sufficiently to be recognized as high-income countries would no longer be subject to the license. Until then, middle-income countries are characterized by highly unequal income distributions. For example, 613 million people in China live on less than \$2 per day.<sup>26</sup> If licenses only enabled generics companies to enter low-income markets, they would leave out many individuals who universities aim to benefit.
- The revenue potential of middle-income countries would help ensure that there are sufficient financial incentives for generic companies to sustain production of a given medicine. Additionally, excluding middle-income countries prevents equitable access provisions from operating where they might work best—for developed-world indications in the developing world. Middle-income countries are in particular need of such medications.<sup>27</sup>

## References

---

- <sup>1</sup> Senate Joint Economic Committee. ‘The Benefits of Medical Research and the Role of the NIH.’ 2000.
- <sup>2</sup> AUTM Licensing Survey: FY 2003.
- <sup>3</sup> Rai A. and Eisenberg S. “Bayh-Dole Reform and the Progress of Biomedicine.” *Law & Contemporary Problems* 2003.
- <sup>4</sup> Michigan State University held IPR. See Eyal Press & Jennifer Washburn, *The Kept University*, *Atlantic Monthly*, Mar. 2000.
- <sup>5</sup> Princeton University holds IPR. U.S. Patent No. 5,344,932 (issued September 6, 1994).
- <sup>6</sup> University of California at San Diego holds IPR. U.S. Patent No. 4,943,533 (issued July 24, 1990).
- <sup>7</sup> Columbia University holds IPR. See <http://www.nih.gov/news/070101wyden.htm>.
- <sup>8</sup> Yale University holds IPR. U.S. Patent No. 4,978,655 (issued on Dec. 18, 1990).
- <sup>9</sup> Emory University holds IPR. See Emory Univ., Office of Tech. Transfer, Product Pipeline 5 (2004), [http://www.ott.emory.edu/shared\\_web/technologies/Emory\\_Pipeline.pdf](http://www.ott.emory.edu/shared_web/technologies/Emory_Pipeline.pdf).
- <sup>10</sup> University of Minnesota holds IPR. See Univ. of Minnesota, Fact sheet on Glaxo-Wellcome AIDS Discovery Settlement (Oct. 5, 1999), [http://www.umn.edu/urelate/newservice/newsreleases/99\\_10glaxofacts.html](http://www.umn.edu/urelate/newservice/newsreleases/99_10glaxofacts.html).
- <sup>11</sup> Emory University holds IPR. See Emory University press release, <http://www.news.emory.edu/Releases/emtri/>.
- <sup>12</sup> Duke University holds IPR. U.S. Patent No. 5,464,933 (issued November 7, 1995); U.S. Patent No. 6,133,418 (issued October 17, 2000)
- <sup>13</sup> Columbia University holds IPR. U.S. Patent No. 4,599,353 (issued July 8, 1986)
- <sup>14</sup> World Health Organization. ‘Scaling up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach.’ [http://www.who.int/hiv/pub/prev\\_care/en/arvrevision2003en.pdf](http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf). 2003.
- <sup>15</sup> Smith, M. “Generic Competition, Price, and Access to Medicines: The Case of Antiretrovirals in Uganda” (Oxfam Briefing Paper No. 26, July 10, 2002).
- <sup>16</sup> Medecins Sans Frontieres. [http://www.doctorswithoutborders.org/news/hiv-aids/briefing\\_doc\\_12-10-2005.cfm](http://www.doctorswithoutborders.org/news/hiv-aids/briefing_doc_12-10-2005.cfm)
- <sup>17</sup> World Health Organization. Brief Meeting Report, Guidelines Development Group. “Antiretroviral drugs for the treatment of HIV infection in adults and adolescents in resource-limited settings.” 2005. [http://www.who.int/3by5/ARVmeetingreport\\_June2005.pdf](http://www.who.int/3by5/ARVmeetingreport_June2005.pdf)
- <sup>18</sup> Strong K. et al. “Preventing chronic diseases: how many lives can we save?” *The Lancet* 2005.
- <sup>19</sup> Andrew Farlow, Oxford University: ‘Costs of Monopoly Pricing Under Patent Protection’, Presentation at Columbia University.
- <sup>20</sup> “HIV Drugs for Africa Diverted to Europe” Washington Post, 3 Oct 2002.
- <sup>21</sup> Outterson, K. “Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets.” *Yale Journal of Health Policy, Law, and Ethics* 2005.
- <sup>22</sup> World Trade Organization. ‘Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health.’ 2003.
- <sup>23</sup> Silker, C. “America’s new war on drugs: should the United States legalize prescription drug reimportation?” *Journal of Legislation* 2005.
- <sup>24</sup> Pharmaceutical Research and Manufacturers of America. ‘Pharmaceutical Industry Profile 2005 – From Laboratory to Patient: Pathways to Biopharmaceutical Innovation.’ Washington, DC: 2005.
- <sup>25</sup> <http://www.worldbank.org/data/countryclass/classgroups.htm>
- <sup>26</sup> Population Reference Bureau. [http://www.prb.org/Template.cfm?Section=PRB&template=/Content/ContentGroups/Datasheets/2005\\_World\\_Population\\_Data\\_Sheet.htm](http://www.prb.org/Template.cfm?Section=PRB&template=/Content/ContentGroups/Datasheets/2005_World_Population_Data_Sheet.htm)
- <sup>27</sup> Yach D. et al. “The global burden of chronic diseases: overcoming impediments to prevention and control.” *JAMA* 2004.