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FEATURE

DRUGS FOR NEGLECTED DISEASES

US incentive scheme for neglected diseases: a good idea gone wrong?

The US priority review voucher scheme was intended to encourage drug companies to invest in treatments for neglected diseases. But nearly seven years on, as **Peter Doshi** reports, there is little demonstrated innovation and evidence that the benefits are not going where they were intended

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Bill Gates believes—or at least believed—that government led market incentives could solve the fundamental conundrum in developing drugs for neglected diseases. For-profit companies see little economic justification to invest in treating diseases that affect the poor, but "creative capitalism," as Gates put it, could lure companies into solving some of the world's most pressing problems by bringing to market new treatments for endemic tropical diseases.

At the 2008 World Economic Forum in Davos, Gates highlighted a new US Food and Drug Administration (FDA) law that rewards sponsors of drugs for tropical diseases with a voucher that entitles the bearer to a "priority review" of another new drug application. "If you develop a new drug for malaria your profitable, say, cholesterol lowering drug could go on the market up to a year earlier," Gates explained. And under the law, the voucher can be sold. "This priority review could be worth hundreds of millions of dollars."

Gates was not the only one to be excited about the idea. Originally proposed by Duke University economist David Ridley and colleagues in the health policy journal *Health Affairs*,[1] the concept was quickly championed by a republican senator from Kansas who, along with two democrat senators, successfully introduced the priority review voucher program into US law. The vouchers are fully transferable between companies and might be worth around $300m (£175m; €220m).

Who is benefiting?

But more than six years later, has this promising concept flopped? Ridley does not think so. "Drug development takes many years (7+) so the impact of the voucher is not immediate." He points to companies that have taken up the charge: "NanoViricides was focused on HIV and flu before learning about the voucher, and now they're developing a drug for dengue."

Nevertheless, the FDA has awarded just three priority reviews vouchers since the law was introduced in 2007: for combination artemether-lumefantrine (Coartem) for malaria, bedaquiline for multidrug resistant tuberculosis, and, most recently, for miltefosine to treat leishmaniasis.

But far from spurring research into new treatments for neglected diseases, two of the three drugs were developed and registered outside the US well before the voucher system was established, meaning that, at least in these cases, the scheme did little to encourage the development of new drugs for neglected diseases.

Miltefosine, for example, has been around for decades. Originally identified as an anticancer compound in the 1980s, the drug came to be used for treating leishmaniasis. Visceral leishmaniasis, the most serious of the three presentations of the disease, kills around 59 000 people a year, making it the "world's second biggest parasitic killer after malaria," according to the World Health Organization.[2] Miltefosine is included in WHO's essential medicines list.

Since 2004, miltefosine has been marketed for the treatment of leishmaniasis in Germany (home of its original manufacturer) and India (where most cases of visceral leishmaniasis occur).[3 4] Before its 2014 approval in the US, miltefosine was also registered in several countries in South America.[5] Licensing and rights to the drug passed through numerous hands over the years: from AstaMedica to Zentaris (which later became AEterna Zentaris). Then in 2008, AEterna Zentaris sold the drug to Paladin, a small Canadian company that was purchased by Endo International for $1.6bn in late 2013.

Miltefosine, however, did not come along for the ride to Endo. By this point Paladin's new drug application to the FDA was well under way and it was expecting approval of miltefosine along with a priority review voucher. Paladin's chief executive, Jonathan Goodman, put a separate price tag on miltefosine, which the company had acquired for $C9m, ($8.5m; £5m; €6.3m) and the expected voucher of more than $100m. Endo refused to pay and so Goodman's new company, Knight Therapeutics, retained the drug. In March 2014, the FDA

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approved miltefosine, making Knight Therapeutics the fourth company to be awarded a priority review voucher.

Following the miltefosine money

But did the voucher go to the right party? Was it right that a drug co-developed with public money and already licensed in key countries should attract such lucrative incentives? The international medical aid organisation Médecins Sans Frontières (MSF) thinks not.

"The PRV [priority review voucher] for miltefosine is not rewarding true innovators," says Julien Potet, a policy adviser at MSF. "Paladin/Knight's efforts have been strictly on regulatory affairs, and we argue that Paladin/Knight should not be rewarded for some preclinical and clinical risks that they did not take."

MSF points out that not only was miltefosine developed well before the voucher program was conceived but neither Paladin (which currently manufactures and markets miltefosine) nor Knight Therapeutics (which holds the licensing rights) even underwrote the drug's research and development. Instead, they note that the clinical trials were funded by a mixture of public and private sources.

Miltefosine has been celebrated as a success story of public-private partnerships.[6] Its development and ultimate registration as a drug to treat leishmaniasis was the product of a near decade-long partnership between industry (first Asta Medica, then Zentaris) and Unicef, the United Nations Development Programme, World Bank, and WHO's Special Programme for Research and Training in Tropical Diseases (TDR). TDR brought knowledge of disease control programs, field experience, and contacts to help build capacity to run the trials as well as money. Industry brought expertise in drug development and money. Together, the partnership resulted in the first oral, single drug treatment for leishmaniasis.[4] While miltefosine's activity against *Leishmania* was known early on, without interest from TDR, the drug would arguably have remained as just a cancer treatment. TDR's involvement in the development of miltefosine achieved the same goal as the FDA's priority review voucher—bringing to market treatments for neglected tropical parasitic diseases.

Pricing

One of the goals of this public-private venture was to ensure miltefosine was an affordable drug. But it is unclear that this goal has been achieved. According to MSF, Paladin charges €2636 ($3570; £2080) for an adult treatment course (€842 for children). It also offers substantially reduced prices (€45-€55 for an adult course) for bulk orders of at least 3500 courses. This, however, presents a problem for MSF.

"It may be possible for a large and highly endemic country like India to reach this quantity, but it is nearly impossible for smaller organisations to reach this quantity. Recently MSF and DNDi [Drugs for Neglected Diseases initiative] had to buy a whole batch together, although this quantity actually exceeded our needs. We are now seeking to donate the drugs that we have bought in excess to third parties. It would be a shame if these drugs expired unused on our shelves," explains Potet.

But Goodman was unsympathetic. He said that MSF "needs to weigh the benefits of the discount against the risk of over-supply."

Reforming the priority review voucher system

Today, Knight Therapeutics is a company with a single product (miltefosine), two employees, $255m in cash, and a priority review voucher. While at Paladin, Goodman bought miltefosine for $9m CAD, which included clinical trial data. FDA approval cost another $10m. And now, Knight hopes to sell the voucher for "a ton of money."

For MSF, Knight's story shows how the priority voucher scheme is a good idea gone wrong. While it strongly agrees with the need for mechanisms to speed development of new treatments for neglected diseases, it questions the wisdom of the law, which allows companies like Knight Therapeutics to singly reap the benefits of the voucher despite the significant public investment in miltefosine's development.

Goodman, however, defends the history. "I find it ironic that MSF would take issue with the PRV program as it is specifically designed to help the same people that MSF is passionately trying to help by encouraging the development of innovative, new therapeutics for neglected tropical diseases." He highlighted the investments his company made: "Paladin spent years and millions of dollars improving the dossier to obtain FDA approval on March 19, 2014. Better lucky than smart!"

A spokesman for the Bill and Melinda Gates Foundation said that although the program has not yet delivered on its original promise, "it's clearly a step in the right direction." He pointed to some theoretical benefits from the law other than novel drugs. "If we do get new formulations, if we do get new manufacturers . . . I think we would see those as benefits as well."

Despite his optimism about the priority review voucher, Goodman acknowledges that the program is—so far at least—a failed policy that has not shown real advances in the treatment of tropical diseases. But for Goodman, this is because the value of the voucher is still unclear and "just theoretical." Of the three vouchers issued, none has been sold. And only Novartis has used its voucher—for an application the FDA ultimately did not approve. Goodman speculates that this financial uncertainty is what has deterred smaller drug companies from developing drugs for tropical diseases. "Until you can demonstrate that the voucher actually has some sort of value, where's the incentive for companies to go out and now specialize in finding treatments for these diseases?" asks Jeffrey Kadanoff, chief financial officer of Knight Therapeutics. (Smaller companies would have no capacity to use the voucher themselves, so would want to sell it to another company with a blockbuster in the pipeline.)

"It's going to sound self serving, but if we do our job well and get a big price tag for this voucher, we will be doing humanity great service. And our shareholders," Goodman says.

In 2010, Duke University's Ridley urged Europeans to adopt a similar priority voucher system.[7] But even Ridley would like to see some changes in the law. While "it's not entirely bad to reward good deeds," he told *The BMJ*, "I favor some changes, including precluding award to drugs approved outside the US several years ago."

Such a change would have kept Knight from its voucher.

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1 Ridley DB, Grabowski HG, Moe JL. Developing drugs for developing countries. *Health Aff* 2006;25:313-24.

2 TDR. Bangladesh beats a deadly scourge, 19 May 2014. www.who.int/tdr/news/2014/deadly_scourge/en/.
3 Æterna Zentaris receives regulatory approval for Impavido® in Germany. Press release, 6 December 2004. www.aezsinc.com/en/page.php?p=60&q=103.
4 TDR. Visceral leishmaniasis elimination. Draft business plan for JCB. 2007. www.who.int/tdr/publications/documents/bl10-business-plan.pdf?ua=1.
5 Shamsuddin H. FDA medical review of application number 204684Orig1s000 IMPAVIDO (miltefosine). 2014. www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204684Orig1s000MedR.pdf.
6 Bryceson ADM. Preface. *Trans R Soc Trop Med Hyg* 2006;100(suppl):S1-S3.
7 Ridley DB, Sánchez AC. Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases. *Lancet* 2010;376:922-7.

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