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Drug Development for Neglected Diseases — The Trouble with FDA Review Vouchers

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September 2008 marked the beginning of a new federal program intended to promote the development of pharmaceutical products for so-called neglected diseases — infectious diseases that disproportionately affect poor populations in developing countries. Implemented by the Food and Drug Administration (FDA) Amendments Act of 2007, this program will give the sponsor of a drug for a tropical disease a "voucher" entitling the company to expedited FDA review of a new drug application for any other product it makes.[1]

The need to encourage additional research in this field is clear. Diseases such as tuberculosis, malaria, leishmaniasis, and trypanosomiasis affect millions of people each year, but these people live primarily in resource-poor settings with underdeveloped health care systems. As a result, the for-profit pharmaceutical industry has invested little in treatments for these conditions. One study found that of the 1393 new chemical entities marketed between 1975 and 1999, only 16 were for such diseases.[2]

The new program links the development of drugs targeting tropical diseases to accelerated approval of a company's other, more profitable drugs for conditions prevalent in wealthier countries. A voucher obtained after the approval of a drug for a tropical disease can be used to require accelerated regulatory review (in 6 months or less) of a cholesterol-lowering drug or an antidepressant, for example, that the sponsor might sell in the United States for thousands of dollars per year of treatment. According to the arrangement's proponents, vouchers could speed up FDA evaluation time by an average of 12 months, providing domestic patients with more rapid access to the latter types of drugs.[3] A voucher could be worth more than $300 million, thanks to the earlier period of market exclusivity afforded by decreasing the time a drug spends in FDA review.

As enacted, however, priority-review vouchers represent an inefficient and potentially dangerous way of encouraging research into tropical diseases. It is inefficient because the program does not directly connect the incentive with the innovation. Large pharmaceutical companies traditionally have not conducted effective research programs on tropical diseases. These manufacturers will be unlikely to start such a program merely because of the prospect of earning a voucher some years in the future, since the voucher's value depends on the success of potential "blockbuster" drugs that are currently in their pipelines, which is far from assured. In fact, tropical-disease research is predominantly conducted by small pharmaceutical companies with limited drug portfolios. Such companies will often be unable to use their vouchers, although the law permits voucher rights to be sold to a large manufacturer. Relying on these sorts of transactions to spur innovation is speculative as well, and the deals between small and large pharmaceutical companies affecting agents of great importance to global health will lack transparency. Such deals may include other payments or exchanges of intellectual property that raise the cost or restrict the future availability of the products.

Another source of inefficiency is that a voucher's value will bear no relation to the usefulness of the drug whose development it is intended to reward. For example, the law stipulates that no voucher will be earned for a product whose "active ingredient" was previously approved. As a result, an effective novel antimalarial

drug that degrades in the heat and must be taken six times a day would earn its sponsor a voucher, but no voucher would be granted for a follow-on formulation that might be more useful in resource-poor settings. Even more problematically, a sponsor rewarded with a voucher for FDA approval of a product for a neglected disease will have no incentive to follow through with implementation of the therapy. After an innovative product is approved in the United States, there can be significant delays before it reaches patients in developing countries, and drug-company ownership of its intellectual property may make it unaffordable. The human papillomavirus vaccine, for example, could be useful in combating cervical cancer in developing countries, but while it remains under patent protection, intellectual property rights and logistic problems have hindered its dissemination in resource-poor settings.[4]

In addition, too-speedy FDA review may lead to bad regulatory decision making. The "priority review" designation was meant to shorten the review time of products that represent major advances in treatment or that treat conditions for which no adequate therapy exists, such as certain types of cancer and infection with the human immunodeficiency virus (HIV). In such circumstances, accelerating the review process is reasonable, given the serious problems faced by patients. But the voucher program will allow drugs for which there is little or no clinical urgency to be subject to accelerated deadlines and may lead to approval of products without adequate consideration by the FDA.

The program reflects a growing trend in health policy toward reliance on substantial financial incentives to achieve a socially desirable outcome — an approach that may have unintended consequences.

The program reflects a growing trend in health policy toward reliance on substantial financial incentives to achieve a socially desirable outcome. Such initiatives may achieve short-term gains, but they do not consistently lead to sustained improvement and may have important unintended consequences. It is especially problematic to rely on pharmaceutical companies' profit motive as the key to developing drugs for resource-poor settings. Effectively conducting research into treatments for neglected diseases involves a more sustained commitment than can be achieved simply by rationalizing the revenue that arises from it. If any changes in the drug-development marketplace, such as initiation of federal drug-reimbursement guidelines in the United States, diminish the perceived value of these vouchers, then any research started solely in anticipation of voucher revenue will again cease, to the detriment of public health.

Though Congress should reconsider the usefulness of the voucher program, there are more direct ways to encourage drug development for medical conditions for which current incentives have proven inadequate. For example, wealthier countries could, in concert with international public health groups, set up independent funds that award reasonable compensation for the development of a safe and useful drug or vaccine and then continue to compensate companies for the appropriate implementation of treatment programs. The level of payment could be adjusted according to the degree of success in controlling the disease in question.[5]

Another alternative would be for governments to work with nonprofit foundations to develop treatments for neglected diseases. The drugs could then be licensed to for-profit pharmaceutical manufacturers for dissemination. Incentives for the manufacturers to become involved could take the form of advance-purchasing promises or grants of extended periods of market exclusivity for such drugs, with accompanying price restrictions to ensure affordability and modest but predictable profits. Precedents exist for such partnerships, including the combined efforts by GlaxoSmithKline and the Bill and Melinda Gates Foundation to create a malaria vaccine and the work of Institute for OneWorld Health, a nonprofit drug-development firm that has produced a treatment for

visceral leishmaniasis and implemented a program to distribute it.

Over the past few decades, the patent system has provided the primary incentive structure for drug development, with the result that needed drugs have not been developed for certain diseases affecting people in resource-poor settings. At the same time, many patients in these environments continue to have inadequate access to important products for more widely prevalent conditions, such as routine immunizations and drugs for cardiovascular disease, cancer, and HIV. It is encouraging to see Congress addressing neglected diseases and taking an interest in an area in which the market has been unable to provide sufficient results. But as the patent system's limitations have shown us, incentives in this field must be narrowly tailored to the desired result and tied to implementation to avoid misuse and to have the greatest effect on global health.

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