Experience With the Priority Review Voucher Program for Drug Development

In 2007, Congress authorized a program intended to promote development of new treatments for neglected tropical diseases, conditions that disproportionately affect poor people in developing countries. Neglected tropical diseases lack treatments for many reasons, including attracting little interest from multinational pharmaceutical manufacturers, which preferentially invest in developing products that offer the possibility for more profitable returns.

To help overcome such barriers, 2007 federal legislation offering priority review vouchers (PRVs) to companies that sponsored drugs newly approved by the US Food and Drug Administration (FDA) to treat qualifying neglected tropical diseases such as tuberculosis, malaria, schistosomiasis, and yaws. Once granted, the vouchers could be transferred or sold, or redeemed at the FDA to accelerate the regulatory review of a different product (eTable in the Supplement) from the standard 10-month period to the priority 6-month period intended to be reserved for drugs that appear to represent therapeutic advances. Earlier access to the US market leads to longer market exclusivity periods and greater revenues. In 2012, PRVs were also made available to sponsors of FDA-approved drugs treating a rare pediatric diseases, with a plan to reexamine the effects of the voucher program in this clinical context after 3 rare pediatric disease vouchers were granted.

Through August 2015, the FDA has issued 6 vouchers (Table). The first tropical disease voucher was granted in 2009 to Novartis for the antimalarial artemether-lumefantrine, even though at the time of FDA approval, this drug had been approved in more than 80 countries. Artemether-lumefantrine qualified because the statute required only that the drug was not yet registered in the United States. To earn the voucher, Novartis submitted to the FDA 8 of the 20 studies it had sponsored from 1993 to 2007 to support approval of the drug abroad.

The next tropical disease voucher was for bedaquiline, indicated for multidrug-resistant tuberculosis. The surrogate measure of efficacy agreed on by the FDA was the rapidity of conversion of patients’ sputum samples from growth to no growth of the tuberculosis bacillus in culture. Although preapproval studies demonstrated an improvement in this measure among bedaquiline-treated patients, those studies also showed a significantly higher mortality (mostly from tuberculosis) for patients treated with bedaquiline than those who were not (10 of 79 vs 2 of 81). Despite these concerns, the FDA approved bedaquiline in 2012 for use “when an effective treatment regimen cannot otherwise be provided.”

In 2014, Knight Therapeutics received a voucher for miltefosine, a treatment for leishmaniasis. Miltefosine was originally developed as an anticancer agent in the 1980s but was found to cure visceral leishmaniasis in the late 1990s. Paladin Laboratories acquired rights to the drug in 2008 for $8.5 million and submitted an application to the FDA for miltefosine in 2013 based on trials it had not conducted dating back to 1999. The drug was approved in 2014. The voucher was sold to Gilead Sciences later that year for $125 million and remains unused.

Three pediatric disease PRVs have been awarded since 2012. The first was issued in February 2014 to BioMarin after FDA approval of elosulfate alfa for the treatment of Morquio A syndrome, an inherited metabolic disease affecting approximately 800 children in the US. The pivotal Phase III trial for the drug was launched in February 2011, 17 months prior to the initiation of the program. This voucher was sold to Regeneron and Sanofi for $67.5 million and used to accelerate the review of alirocumab, a PCSK9-inhibitor approved in July 2015 for patients with familial hypercholesterolemia.

In March 2015, 2 additional rare pediatric disease vouchers were awarded. The first was granted to Asklepios Pharmaceuticals, the sponsor of cholic acid, approved for the treatment of bile acid synthesis disorder. The efficacy and safety of cholic acid was demonstrated in an investigator-initiated trial begun in 1994. After approval, the rights to the drug and voucher were obtained by Retrophin, which subsequently sold the voucher to Sanofi for $245 million in May 2015.

The most recent voucher was granted to United Therapeutics for approval for dinutuximab, a drug for combination use with other treatments for pediatric patients with high-risk neuroblastoma. This drug was developed by the National Cancer Institute, which synthesized it, conducted its initial preclinical studies, and then manufactured it through the Biopharmaceutical Development Program to perform pivotal phase 3 testing between 2001 and 2009. In August 2015, United Therapeutics sold its voucher to AbbVie for $350 million.

Based on this experience, some preliminary conclusions can be drawn about the PRV program. First, little reliable evidence that the program’s primary intention of spurring novel drug development has been met exists, at least for tropical diseases, for which PRVs have now been available for 7 years. Artemether-lumefantrine was registered worldwide prior to FDA approval. Miltefosine was registered outside the United States a decade before its FDA review. The sponsor of its FDA application earned the voucher despite not being involved in its development. Artemether-lumefantrine, miltefosine, dinutuximab, and cholic acid were also based on significant public sector investment. One way to potentially prevent such windfalls would be to redesign the voucher system so that drug companies would have to show some level of investment in a new drug’s development before earning the reward.
The voucher may have had limited influence on drug development so far because its value only accrues after drug approval. The development process can be uncertain and may take 6 to 10 years or more from the time of original molecule identification. The voucher may be optimally useful for cases like artemether-lumefantrine or miltefosine—drugs that are known to be effective but have not been taken through the final step to FDA approval for reasons that could include the relatively minor costs of drug registration. Experience with the program, though, suggests that few effective and safe drugs for tropical diseases are undeveloped and could be taken through any final steps but for the additional late-stage incentive that the vouchers provide.

The value of the voucher has increased from $67.5 million to $350 million. The prospect of a payment of as much as $350 million a decade or so in the future may nevertheless be insufficient for large pharmaceutical manufacturers accustomed to substantially higher revenues to change their investments to tropical or rare pediatric diseases. For instance, Sanofi, which was involved in the purchase of 2 vouchers, reported revenues of more than $43 billion in 2014. Nonprofit drug manufacturers may be in a better position to take this value into account. Medicines Development recently announced plans to earn a voucher by seeking FDA approval of moxifloxacin for tuberculosis, with the occasion to reexamine whether the program has actually met its goals or tailoring it to better reward true innovation and ensure affordable access to life-saving therapies.

Whether the voucher is successful at improving drug innovation, it clearly does not ensure affordable access to the products either in the United States (elosulfase costs $380 000 per year7) or overseas. As a result, making use or sale of the voucher conditional upon demonstrating equitable marketing of the drug has been suggested.8 For example, differential pricing across countries is commonly used to make treatments available in resource-poor settings, having successfully reduced the cost of antiretroviral human immunodeficiency virus and AIDS in developing countries by up to 90% of the profit-making price charged in high-income countries. The voucher program could be further amended to make its issuance dependent on successful demonstration of such a plan.

Several more promising approaches exist to promote discovery of new treatments for neglected tropical diseases or other overlooked disease classes. In particular, greater funding of basic science research would help identify novel targets for therapy. Yet despite little evidence of its benefits, the voucher remains politically popular because it lacks direct public financing by taxpayers. In 2015, the US House of Representatives passed legislation to perpetuate the rare pediatric disease voucher program instead of using the occasion to reexamine whether the program has actually met its goals or tailoring it to better reward true innovation and ensure affordable access to life-saving therapies.

### Table. Awarded Priority Review Vouchers, September 2008 to August 2015*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Sponsor</th>
<th>Disease</th>
<th>Sold</th>
<th>Used</th>
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<tbody>
<tr>
<td><strong>Neglected tropical diseases</strong></td>
<td></td>
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<tr>
<td>Artether-lumefantrine</td>
<td>2009</td>
<td>Novartis</td>
<td>Malaria</td>
<td>No; used internally</td>
<td>Canakulinab for gouty arthritis in 2011 (indication rejected)</td>
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<tr>
<td>Bedaquiline</td>
<td>2012</td>
<td>Johnson &amp; Johnson</td>
<td>Multidrug-resistant tuberculosis</td>
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<tr>
<td>Miltefosine</td>
<td>2014</td>
<td>Knight Therapeutics</td>
<td>Leishmaniasis</td>
<td>$125 million to Gilead Sciences, 2014</td>
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<tr>
<td><strong>Rare pediatric diseases</strong></td>
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<tr>
<td>Elosulfate alfa</td>
<td>2014</td>
<td>BioMarin</td>
<td>Marquio A syndrome</td>
<td>$67.5 million to Regeneron and Sanofi, 2014</td>
<td>$67.5 million to Sanofi, 2015</td>
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<tr>
<td>Cholic acid</td>
<td>2015</td>
<td>Asklepios*</td>
<td>Bile acid synthesis disorders involving single-enzyme defects and peroxisomal disorders</td>
<td>$245 million to Sanofi, 2015</td>
<td></td>
</tr>
<tr>
<td>Dinutuximab</td>
<td>2015</td>
<td>United Therapeutics</td>
<td>High-risk neuroblastoma</td>
<td>$350 million to Abbvie, 2015</td>
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* Rights to approved drug and voucher subsequently purchased by Retrophin for approximately $40 million.

### References