

POINT/COUNTERPOINT

Drug and Vaccine Development for Infectious Diseases: The Value of Priority Review Vouchers

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Priority review vouchers (PRVs) are an innovative, high-impact, low-cost mechanism for encouraging the development of new medicines and vaccines for infectious diseases. Infectious diseases kill more than 14 million people per year—around a quarter of deaths worldwide.¹ For many of these diseases, cost-effective drugs and vaccines do not currently exist, and less than 15% of molecules reported to be under development are anti-infectives (i.e., vaccines or therapeutics targeting infectious diseases).² This neglect is due in large part to the unfavorable economics surrounding anti-infectives.

Pharmaceutical firms have a fiduciary responsibility to shareholders to maximize profits. Absent other incentives, firms will invest in research and development (R&D) for products that possess a profitable market and a high likelihood of technical success. In contrast, the global burden of infectious diseases is concentrated in developing countries with small budgets and weak patent protection, among poor patients who can pay only low prices for drugs—or cannot pay at all. Anti-infectives are thus typically not profitable products. In addition, the probabilities of technical success at each R&D stage are lower for anti-infectives than for most other pharmaceuticals, making R&D investments in anti-infectives high-risk.³ Market failures surround anti-infectives because of their positive externalities:

for instance, your receipt of a vaccine reduces not only your risk of disease but also mine, yet I do not compensate you or the vaccine producer for the benefit I gain. Thus, private investment in R&D for anti-infectives is below the level that would be socially optimal.

Several approaches to increasing R&D for anti-infectives have been implemented, including government and foundation funding for R&D, the Orphan Drug Act provisions, and purchase agreements such as advance market commitments. The PRV, a cost-effective addition to these incentives, was originally proposed by Ridley *et al.*⁴ and later established in law under the Food and Drug Administration (FDA) Amendments Act of 2007 (Public Law 110-85).

Under the law, a PRV is awarded to a successful developer of a New Molecular Entity that receives FDA approval and targets any one of 16 tropical diseases listed in the law or “any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by regulation by the [Department of Health and Human Services (HHS)] Secretary.” (Of importance, what qualifies as a “significant market” is not defined in the law.) The developer can then hold the PRV or sell it to another firm. The PRV entitles its holder to FDA priority review of any drug in its portfo-

lio that otherwise would receive standard review. Priority review shortens an FDA review period by several months, by concentrating more FDA resources on an application. With a shorter review, a product is marketed earlier than it otherwise would be. In most cases, the product does not produce more revenue as a result, but because the revenues are received sooner—and firms, like individuals, prefer to receive money sooner rather than later—the “net present value” of the revenues is higher.

By one estimate, the net present value of a PRV to a firm is around \$300 million when applied to a blockbuster product that has annual global revenues of US\$1 billion or more (in the 1990s, 29 blockbusters were launched).⁴ Because a PRV is transferable, an innovative biotechnology company could develop a tropical disease product, earn a PRV, and sell it to a pharmaceutical firm that has a blockbuster in its pipeline. The exact value of a PRV will depend on the number awarded, the number and expected value of potential blockbusters, and the difference between standard and priority review times. (In 2007, the difference between median standard and priority review times for New Molecular Entities and Biologic License Applications was 7 months.⁵) In our own conversations with pharmaceutical and biotechnology companies, estimates of a PRV's value ranged from less than \$100 million

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to more than \$500 million. No PRVs have yet been awarded, so their value remains an open question.

To prevent delayed reviews of other medically important products, the FDA would, ideally, need to hire additional staff to review PRV holders' products. The cost of this additional labor has been estimated at \$1 million per product and is billed to the firm that exercises the voucher.⁴ The FDA PRV program allows the agency to set the fee each year, ensuring that the government is adequately compensated for the added labor. Because a PRV increases the value of a tropical disease product by hundreds of millions of dollars, at a net cost to the public of approximately zero, the PRV is highly cost-effective.

We are aware of only a few published negative critiques of the PRV program. Goozner⁶ argued that PRVs will cause first-world consumers to pay substantially more for drugs than they otherwise would because, in his view, the PRV extends a drug's effective patent life. In fact, PRVs are not expected to have this effect. Under the Hatch–Waxman Act, the duration of FDA review is added back to a drug's effective patent life—the patent life remaining after a product is marketed—with conditions on the maximum restoration allowed. As a result, priority review usually has no effect on effective patent life: whatever time is lost under standard review is added back, and whatever time is gained under priority review does not alter the patent's expiration date.

Around 10% of drugs have long clinical trial and review periods that “max out” the Hatch–Waxman provision,⁷ and for these drugs priority review can increase effective patent life up to several months. But even in these cases, priority review does not delay the introduction of generics. Effective patent life is lengthened by beginning earlier, rather than by ending later, so generics are introduced no later than they otherwise would be. In most cases, consumers will have access to both a branded product and a generic product sooner than they otherwise would.

Kesselheim^{8,9} expressed concern that products receiving priority review

under a voucher may not be adequately evaluated because of time pressures on FDA staff. However, as Moe *et al.*¹⁰ note, priority review “does not omit safety or efficacy studies or require approval within a given time frame.” There is a 6-month target for priority review, but actual review times are as long as needed. Moreover, there is no consistent evidence that shorter review times at the FDA are associated with safety problems.¹¹ A challenge in implementing the new PRV program will be expanding the pool of qualified FDA personnel for additional priority reviews. This challenge can be met but will need to be part of the broader effort at the FDA to increase review capacity.

The FDA is reviewing public input regarding diseases that could qualify for PRVs in addition to the 16 tropical diseases named in the law. As noted previously, section 524 of the law allows the FDA to designate by regulation any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized countries. Products for emerging infectious diseases are natural candidates, as are products for neglected diseases such as Chagas disease and *Shigella*. Biodefense products could also be eligible for PRVs, because Ebola, typhus, and other potentially weaponizable diseases have no significant market in developed nations and disproportionately affect poor countries. These products suffer the same market failures that affect tropical diseases, and although some government funding exists, it is insufficient to cover the costs of drug and vaccine development. By one estimate, the current US government funding for advanced development of biodefense products is less than 10% of what is needed to meet the HHS Public Health Emergency Medical Countermeasures Enterprise requirements.¹²

Expanding eligibility for PRVs beyond the current 16 tropical diseases would help accelerate the development of many other pharmaceuticals needed to reduce death and disease worldwide. In reviewing existing and proposed incentives for anti-infective R&D, we concluded that the PRV is among the

most efficient.¹³ PRVs alone will not be sufficient to generate all the pharmaceuticals the world needs. There is still an urgent need to invest in basic research on infectious diseases and in product-development partnerships for drug and vaccine development. Although PRVs may play a modest role compared with these other efforts, they are a valuable and highly cost-effective addition.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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