By David B. Ridley and Stephane A. Régnier

The Commercial Market For Priority Review Vouchers

David B. Ridley (david.ridley@
duke.edu) is the faculty
director of the Health Sector
Management Program, Fuqua
School of Business, at Duke
University, in Durham, North
Carolina.

Stephane A. Régnier is a
global director of health
economics outcomes research
for Novartis Pharma AG, in
Basel, Switzerland.

ABSTRACT In 2007 the US Congress created the priority review voucher program to encourage the development of drugs for neglected diseases. Under the program, the developer of a drug that treats a neglected disease receives both a faster review of the drug by the Food and Drug Administration and a voucher for a faster review of a different drug. The developer can sell the voucher. We estimated the commercial value of the voucher using US sales of new treatments approved in the period 2007–09. A third of the commercial value of a voucher comes from capturing market share from competitors, nearly half from the value of earlier sales because of the expedited review, and less than a quarter from lengthening the time between approval and the launch of a generic competitor. We estimate that if only one priority review voucher is available in a year, it will be worth more than $200 million, but if four vouchers are available, the value could fall below $100 million. Congress should be cautious about expanding the voucher program, because increasing the number of vouchers sharply decreases the expected price. Lower voucher prices could undermine the incentive to develop new medicines for neglected diseases.

The standard review of a new drug by the US Food and Drug Administration (FDA) takes about ten months. However, the FDA offers priority review—which takes about six months—to drugs that provide significant improvements in safety or effectiveness over existing drugs. The difference of four months in review times could be highly valuable to a drug developer with a potential blockbuster drug.[1]

In 2007 Congress leveraged the value of an earlier FDA approval by creating the priority review voucher program to encourage the development of new drugs for neglected diseases. And in 2012 Congress expanded eligibility for priority review vouchers to include rare pediatric diseases. Under the voucher program, the developer of a drug for a neglected or rare pediatric disease receives priority review for that drug, as well as a bonus priority review voucher for another drug treating any disease. Thus, the following two drugs are involved: the drug that earns its manufacturer a bonus priority review, and the drug that uses that bonus priority review. The drugs need not be from the same company, because the voucher may be sold. The ability to sell a voucher increases its value, especially for smaller firms with fewer drugs.[2]

The objectives of this article are to estimate the commercial value to the potential buyer of a priority review voucher, based on current regulatory and market conditions, and to show how the voucher price falls as the quantity of available vouchers increases. The price of a priority review voucher is critical to the success of the program in encouraging new drug development.[3]

As of the end of 2015 nine vouchers had been awarded, and four of them had been sold. Vouchers were awarded for drugs for neglected diseases, including malaria and leishmaniasis, as

well as rare pediatric diseases.[4]

Chief executives of small drug development companies report that the voucher incentive was instrumental in allowing them to secure financing for drugs for neglected diseases, including dengue and river blindness.[4] These drugs are currently under development and are expected to be submitted to the FDA in the future. Treatments for diseases such as dengue and river blindness tend to be neglected by drug developers because most of the people suffering from the diseases live in low-income countries.[5,6]

Prices of the vouchers that were sold ranged from $67.5 million in July 2014 to $350 million in August 2015.[7] The variation in price suggests considerable uncertainty about the market price for a voucher. This uncertainty is consistent with the literature on priority vouchers.[8] Jason Matheny and colleagues reported that estimates of a voucher's value ranged from less than $100 million to more than $500 million.[9] Similarly, Andrew Robertson and coauthors reported that for the large companies they surveyed, estimates of voucher sales prices ranged from less than $50 million to more than $400 million.[10]

We estimated the value of a priority review voucher based on the value of the following three effects: capturing market share from competitors; having earlier sales of a new drug; and, when applicable, having more time on the market before the entry of a generic competitor. No previous studies have estimated the value of all three effects. Instead, they have tended to focus on the value of one effect, such as having earlier sales[1,11] or capturing market share from competitors.[12]

Furthermore, we updated previous research that based the value of the voucher on standard FDA regulatory review times that exceed recent observations. While it has consistently taken the FDA about six months to complete a priority review, the average standard review time has decreased from about eighteen months in the 1990s[1] to fifteen months in the early 2000s[13] and ten months in the early 2010s.[14] Therefore, a voucher today saves less time and thus has less value than previous estimates suggested. The changing regulatory and commercial environment necessitates a new analysis of the value of a voucher.

We also examined how the priority review voucher price falls with the availability of additional vouchers. This price reduction can drive down the incentive to develop drugs for neglected diseases already on the eligibility list for vouchers. The effect on a voucher price is important for policy makers.

For example, Congress is considering the Medical Countermeasure Innovation Act, which would expand eligibility for the vouchers to include medical countermeasures, such as treatments for anthrax.[15] There is some danger that Congress will view the voucher program as a success and therefore expand it, thus undermining its future success. With more priority review vouchers available, the average value of a voucher is reduced, as is the incentive to develop innovative new medicines for neglected and rare diseases.

Study Data And Methods

Faster review creates value for the manufacturer through the following three effects: taking market share from competitors, having earlier sales, and having more time on the market before the entry of a generic competitor. We call the first effect the *competitive effect*. Early movers can take market share from competitors, because drugs that reach the market sooner than their competitors tend to lock in consumers and have a sustained higher market share.[12] The second effect is the *time value effect*: Sales generated earlier are more valuable than sales generated later, in part because the money from sales can be invested and earn a return. The third effect is the *exclusivity effect*: The earlier a drug is launched, the more time it may have on the market without generic competition.

After estimating the priority review voucher value based on these three effects, we estimated the price of a voucher. The price will be less than the value if there are many sellers and if the voucher value varies across potential buyers.

DATA We were interested in the value of a priority review voucher for a drug that would otherwise receive a standard review at the FDA. Hence, we excluded from our sample drugs that did not have standard review—that is, drugs given priority review by the FDA because they offered a significant improvement in safety and effectiveness compared to current drugs.

To estimate the competitive effect of the voucher, we used data and an analysis that were consistent with those we used previously.[12] And as we did previously,[12] we used sales data from the National Prescription Audit and promotional spending data from SDI Health.[16]

To estimate the time value and exclusivity effects of a voucher, we collected US net sales of forty-four new molecular entities or new biologics that were approved by the FDA in the period January 1, 2007–December 31, 2009, and that had a standard review. We considered approvals only from 2009 and earlier so that we would have five years of sales data. Our main data sources were the drug manufacturers' annual reports. Sales reported in these annual reports are typi-

cally net of rebates. In instances where net sales were not available in annual reports, we used analysts' reports or sales reported by IMS Health.

We converted net sales to 2014 dollars using the prescription drug index of the Consumer Price Index—All Urban Consumers. As Ernst Berndt and colleagues did,[17] we projected future sales for recently launched drugs. We predicted future sales using the prescription uptake curve of twenty-six standard-review products, fifth-year sales, and an annual price increase of 3.2 percent (the compounded average growth rate for the period 2009–14 of the prescription drug index of the Consumer Price Index—All Urban Consumers). We estimated sales for twenty years after submission to the FDA.

ESTIMATING THE COMPETITIVE EFFECT First, we estimated the competitive effect, in which value comes from earlier market entry relative to the entry of competitors within the same therapeutic area. A drug with earlier market entry is adopted by more providers and patients than a drug with a later entry, and if the first drug is effective for those patients, they are reluctant to switch to a later market entrant. Hence, earlier market entry yields higher sales.

To estimate the competitive effect, we used the same approach that we did previously,[12] when we estimated peak share (that is, the highest monthly market share within the first four years after launch) as a function of speed to market, promotional spending, order of market entry (for example, whether the drug entered second or third in its therapeutic class), and number of competitors. We then used the increase in peak share from launching four months earlier to estimate the increase in annual sales that would result from having a priority voucher. More information about our estimation of the competitive effect is available elsewhere[12] and in the online Appendix.[18]

ESTIMATING THE TIME VALUE AND EXCLUSIVITY EFFECTS Second, we estimated the time value effect, meaning the value of generating earlier sales. Earlier sales are more valuable than later sales in part because, as noted above, the money from sales can be invested. We assumed a cost of capital of 10.5 percent.[19] As discussed above, we estimated sales for the twenty years following submission to the FDA, including zero sales during review. In a sensitivity analysis, we used a different cost of capital and a time horizon beyond twenty years.

Third, we estimated the exclusivity effect. Compared to a drug that receives a standard review, a drug with a priority review voucher is approved earlier, but its patent does not necessarily expire earlier. This means that it can have a longer period of time between drug launch and

patent expiration, which we refer to as the effective patent life. Under the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Act), the patent expiration date depends on the length of clinical testing and review (for more on the patent term and how it affects voucher value, see the Appendix).[18]

In addition to the assumptions described above, to calculate the time value and exclusivity effects, we made the following assumptions, which are summarized in Exhibit 1: that the probability of approval of a drug for which a voucher would be used was 90 percent;[19] that the marginal corporate tax rate was 28 percent;[20] that the marginal cost of making a drug was 20 percent, based on the ratio of the price of generic drugs to brand-name drugs when there are many generic competitors;[21] that the time between the purchase of a voucher and submission for FDA approval was six months (which means that approval would come twelve months after the purchase of a voucher, as was the case when Regeneron/Sanofi purchased a voucher for alirocumab, its cholesterol drug);[22] that the drug would have market exclusivity of 12.9 years, with a standard deviation of 3.2 years;[23] and that after patent expiration, brand-name sales would erode, falling to 11 percent of the molecule market share as of one year after the entry of a generic competitor (with 9 percent as the standard deviation).[23] In a sensitivity analysis, we modified the erosion rate to examine how the value of a voucher would increase with limited generic competition, as could happen with biologics.

VOUCHER PRICE To estimate the voucher price, we estimated the value of a voucher for each drug approved in a given year after a standard review. We ordered the values of these vouchers from highest to lowest in a given year and then estimated the range of possible voucher prices: For

The changing regulatory and commercial environment necessitates a new analysis of the value of a voucher.

Assumptions used to estimate the value of a priority review voucher

| Description	Value	Source
Voucher acceleration of regulatory review	4 months	FDA goals are 6 months for priority review and 10 months for standard review (see Note 14 in text)
Fifth-year sales for a top-selling drug	$914 million	Authors' analysis of data on average sales of lisdexamfetamine, regadenoson, ustekinumab from company annual reports
Discount rate	10.5%	DiMasi et al., 2016 (see Note 19 in text)
Market exclusivity with voucher	12.9 years	Grabowski et al., 2014 (see Note 23 in text)
Probability of approval after submission	90%	DiMasi et al., 2016 (see Note 19 in text)
Marginal cost	20%	Grabowski et al., 2007 (see Note 21 in text)
Tax rate	28%	Mintz and Chen, 2014 (see Note 20 in text)
Brand share of molecule 12 months after generic entry	11%	Grabowski et al., 2014 (see Note 23 in text)
Time between voucher purchase and FDA decision	12 months	Sanofi/Regeneron purchased a voucher in 2014; the FDA decision was in 2015 (see Note 4 in text)
Time horizon	20 years	Authors' assumption
Annual price increase	3.2%	Authors' analysis of data from the prescription drug index of the Consumer Price Index—All Urban Consumers

SOURCE Authors' analysis of data from the sources in the exhibit. **NOTE** FDA is Food and Drug Administration.

each voucher, the price could be as high as the voucher value and as low as the value to the alternative buyer (alternative buyers are discussed below). We assumed that the relevant time period was one year (that is, we estimated the potential voucher value and prices per calendar year).

Estimated value of a priority review voucher by its three effects
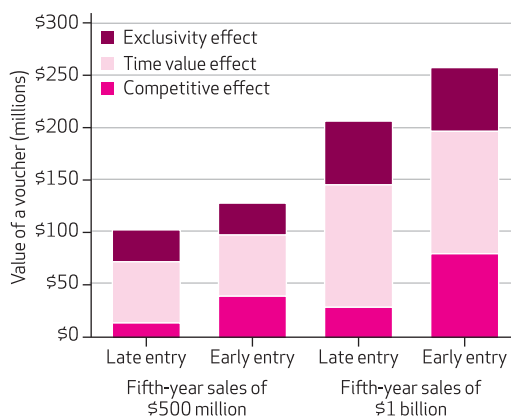
SOURCE Authors' analysis using the assumptions in Exhibit 1. **NOTES** The value of the priority review voucher is divided into three effects—competitive effect, time value effect, and exclusivity effect (explained in the text)—according to whether the fifth-year sales are $500 million or $1 billion and whether the drug in question is first or second to enter the market (early entry) or third (late entry).

For example, consider three drugs for which the value of priority review would be $300 million, $200 million, and $100 million, respectively. If there were just one voucher for sale, the bidder that values the voucher at $300 million would buy the voucher, and the bidder that values the voucher at $200 million would be the alternative buyer. We expect the price to be between $200 million and $300 million, because at prices below $200 million, two bidders (the manufacturers of the drugs for which the voucher would have a value of $200 million or $300 million) would bid up the price to $200 million, and at prices above $300 million no one would be willing to purchase the voucher. Likewise, if there were two vouchers for sale, then we would expect the price to be at least $100 million.

Additional details about the theoretical model, estimation methods, and sensitivity analyses are available in the Appendix.[18]

Study Results

COMPETITIVE EFFECT For the first or second drug in the same therapeutic area to enter the market, accelerating drug launch by four months is associated with an increase in peak share of 1.2 percentage points (for example, from 50 percent to 51.2 percent).[12] If two drugs launch at the same time, each drug is expected to achieve 50 percent peak share in the first four years, so 1.2 percentage points would be a 2.5 percent increase in sales. Similarly, for the third drug to enter the

EXHIBIT 3

Priority review voucher value based on fifth-year sales and approval acceleration

Millions of dollars

Fifth-year sales	Approval acceleration (months)						
	1	2	3	4	5	6	7
$ 250	$ 28	$ 40	$ 52	$ 64	$ 76	$ 87	$ 99
500	56	81	105	128	151	175	197
750	85	121	157	192	227	262	296
914	103	147	191	234	277	319	361
1,000	113	161	209	256	303	349	395
1,250	141	202	261	320	379	436	493
1,500	169	242	314	384	454	524	592
1,750	197	282	366	448	530	611	691

SOURCE Authors' analysis using the assumptions in Exhibit 1. **NOTE** The exhibit shows the voucher values only for drugs that were first or second entrants into the market and whose effective patent life would be extended by the duration of the accelerated review time.

market, accelerating drug launch by four months is associated with an increase in sales of less than 1 percent (or 0.30 percentage point).

EXPECTED VOUCHER VALUE FOR TOP-SELLING DRUGS The value of the voucher depends on many factors, including entry order and effective patent life, denoted in Exhibit 2 as the exclusivity effect, and approval acceleration (Exhibit 3). For a drug that has fifth-year sales of $1 billion and is an early mover to the market (which means no competing drug has locked in many providers and patients), the voucher value is $256 million if the drug extends effective patent life and $196 million if it does not (Exhibit 2).

For a drug that has fifth-year sales of $914 million (the average for the top-selling drugs of

EXHIBIT 4

Value of priority review vouchers, by number of vouchers issued per year

SOURCE Authors' analysis of products approved in the period 2007–09 with a standard review by the Food and Drug Administration. **NOTES** The expected price is between the value to the buyer and the value to the alternative buyer. If there are two vouchers available, there will be two buyers (those willing to pay the first- and second-highest prices; the alternative buyer will be the one not willing to pay either of those prices).

2007, 2008, and 2009), the voucher value is $234 million if the voucher extends the effective patent life by four months (Exhibit 3). Of that value, almost half ($106 million) is attributable to the time value effect, roughly a third to the competitive effect ($73 million), and less than a quarter to the exclusivity effect ($55 million). The voucher value decreases to $179 million if the voucher does not extend the drug's effective patent life (data not shown).

If the drug that benefits from priority review is the third to enter the market instead of the first or second, the voucher value decreases from $234 million to $189 million (assuming that potential fifth-year sales remain at $914 million). This is because of the reduced competitive effect of an earlier approval of a drug on third entrants into the market, compared to second entrants ($27 million versus $73 million).

If a drug has potential fifth-year sales of $250 million and the voucher extends the effective patent life by the four months provided by the priority review, the voucher value for a first or second entrant into the market decreases to $64 million (Exhibit 3). If a product reaches blockbuster status at that time instead (sales of $1 billion), the voucher value is $256 million.
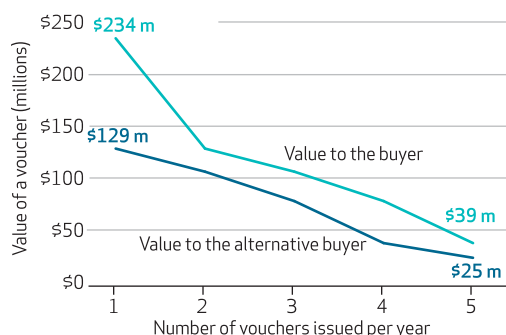
We assumed that generic competition eroded fourteenth-year and later sales. However, the assumption has little effect on the present value of a voucher, because sales in the distant future are heavily discounted. Without generic competition, the voucher value increases from $234 million to $263 million (data not shown). Likewise, the voucher value increases from $234 million to $267 million if the discount rate is 8 percent instead of 10.5 percent. Extending the analysis from twenty years to twenty-five years after FDA submission increases the voucher value by less than $2 million.

VOUCHER VALUE AND PRICE If there were only one voucher to be sold per year, the value of the voucher would be between $234 million (the value to the buyer willing to pay the highest price) and $129 million (the value to the buyer, known as the alternative buyer, willing to pay the second-highest price) (Exhibit 4). The steep decline in value as the number of vouchers increases is a result of a skewed sales distribution. The highest-grossing drug has sales that are nearly double those of the second-highest-grossing drug ($900 million compared to $500 million, as shown in the Appendix).[18]

In Exhibit 4 we assumed that the patent expiration date was unchanged, so that a voucher gave a drug an extra four months of effective patent life. However, if the voucher moved the expiration date forward, the voucher value and price would both fall by about 25 percent.

The estimates presented here apply to the economic value of earlier drug launch in general.

BUSINESS IMPLICATIONS OF THE VOUCHER VALUE We showed that the expected value of a voucher for a drug with $914 million in fifth-year sales is $234 million (assuming an exclusivity effect). If four vouchers are available in one year, our estimates predict prices as low as $39 million (the value to the would-be fifth buyer). If there is one price for all four vouchers, the price will be between $39 million and $79 million. If there is not a single price for all four vouchers, perhaps because the voucher sellers and buyers are not all in the market at the same time, the price could be as high as $234 million.

How do the estimates compare to actual selling prices? Recall that vouchers have been sold for prices ranging from $67.5 million in 2014 to $350 million in 2015.[7] Regeneron paid $67.5 million for a voucher to speed the review of alirocumab, which suggests that Regeneron expected sales of the drug to exceed $250 million. Indeed, before alirocumab's launch, analysts projected fifth-year sales of more than $1 billion in the United States.[24] Thus, the value of the voucher would be more than $256 million (Exhibit 3)—well in excess of the price of $67.5 million paid by Regeneron.

AbbVie paid $350 million for a voucher to be used in the future on an unspecified drug. A $320 million voucher price is associated with fifth-year US drug sales of $1.25 billion (Exhibit 3), so clearly AbbVie expected the voucher to be used for a blockbuster drug. Moreover, because only one voucher was available at the time, the price suggests that the voucher had a high value to both AbbVie and another bidder.

Whether the voucher will provide a positive return for the developer depends on whether the expected net present value of a voucher exceeds the cost of conducting a Phase III clinical trial. The expected net present value of a voucher sold for $234 million is approximately $99 million at the beginning of such a trial. This estimate assumes that only a Phase III trial is required, the probability of submission is 70 percent, the probability of approval is 90 percent, the discount rate is 10.5 percent, and four years elapse between the beginning of the trial and FDA approval.[19,25]

A net present value of $99 million will typically cover the cost of a Phase III trial plus FDA submission for a drug for a parasitic or infectious disease. While the average out-of-pocket cost for such a trial and submission is $190 million,[25] the cost of a trial for an anti-parasitic or anti-infective drug tends to be about half of the average,[26] and orphan drug tax credits cut those costs in half again. Therefore, a voucher price of $234 million should cover the cost of a Phase III trial plus FDA submission.

If voucher prices fall below $100 million, as we would expect with four or more vouchers per year (Exhibit 4), then the expected net present value of the voucher would fall below the cost of a Phase III clinical trial. Hence, the voucher (even with orphan drug tax credits) would not provide sufficient incentive for drug development, and additional incentives would be needed—such as an advance market commitment[5] or a profitable commercial market.

Finally, while the focus of this article is on the priority review voucher program, the estimates presented here apply to the economic value of earlier drug launch in general. Thus, they are relevant for estimating the economic gains from faster completion of clinical trials and faster FDA review.

LIMITATIONS

▶ **LIMITATIONS OF THE MODEL:** There are several reasons why the potential voucher value could be higher than the value in our model. First, the competitive effect value would double if two companies were racing to have the first drug approved in a class and only one voucher were available. In such a race, the competitive effect of a voucher would include not only the impact on its buyer's drug, but also the impact of preventing the competitor from increasing its drug's market share through earlier market entry. The competitive effect would double from $80 million to $160 million and the voucher value would rise from $256 million to $336 million for an early entrant with fifth-year sales of $1 billion (Exhibit 2).

Second, the voucher value would be higher than our estimates if drug sales were higher than the sales of the drugs in our data sample. Our three-year sample period (2007–09) did not include mega blockbuster drugs such as atorvastatin and esomeprazole magnesium that achieved multiple billions of dollars in annual sales while under patent protection.

Third, if one company controlled the market for vouchers, either through its own drug development or through buying vouchers from

others, then it could charge higher prices than we estimated. Similarly, while many vouchers might be sold in a given year, if a company had only a small window of time during which to purchase a voucher (that is, between receipt of the results from a Phase III clinical trial and submission to the FDA), and only one voucher were available during that window of time, then the seller would have market power and the price might be close to the buyer's value.

Conversely, recall that the voucher value would be lower if there were no exclusivity effect (Exhibit 2). Also, the voucher value would be lower if earlier market entry did not translate to earlier sales because of delays by payers waiting to grant reimbursement until a competitor drug entered the market.

▶ LIMITATIONS OF THE VOUCHER PROGRAM: This article has focused on the commercial value of the priority review voucher program. However, there are several concerns about the social value of the program. First, vouchers have been awarded for drugs that would have been developed without the incentive.[27] This is analogous to giving tax breaks for charitable donations that would have been made even without the tax incentive. However, unlike tax breaks, the costs of the voucher program are not necessarily borne by the government. In some cases, the costs of the program are borne by competing drug companies that lose market share to the company that uses the voucher for its drug. Regardless of who bears the costs, it appears that some voucher recipients received a windfall. One possible regulatory mechanism for reducing such windfalls would be to require a minimum investment in research and development by voucher recipients. However, such cost-based rewards might encourage inefficient investment.

Second, while the voucher program encourages innovation, it does not ensure access to drugs developed as a result of the program.[1,27–29] Drug developers should be required to submit to FDA their plans for how to make their drugs accessible. Also, funding from governments or foundations might be needed to purchase treatments for people with neglected diseases who live in low-income countries. Other mechanisms for encouraging drug development for neglected diseases include direct government or foundation subsidies of clinical trials and advance commitments to purchase the drugs.[5,30]

Policy Implications

As more diseases are included in the priority review voucher program, the number of vouch-

Congress and the FDA should carefully consider the conditions for eligible diseases and drugs.

ers will increase. However, we have demonstrated how eligibility expansion could decrease the expected vouchers' price and reduce the incentives to invest in neglected or rare pediatric diseases.

If four vouchers were granted per year for products that would otherwise receive standard review, the price of a voucher could fall as low as $39 million (Exhibit 4). The net present value would be even lower and might not cover the cost of a Phase III clinical trial. Because a lower price for vouchers would reduce the incentive for developing drugs for these diseases, policy makers should think carefully about making additional diseases eligible for vouchers.

To avoid the substantial decline in the price and value of priority review vouchers that would be caused by having a large number of vouchers in the marketplace, Congress and the FDA should carefully consider the conditions for eligible diseases and drugs. Additional diseases should be evaluated for inclusion in the program based on need—which might include factors such as the burden of the disease, current drugs in use or in late-stage development, and alternative incentive mechanisms. Furthermore, Congress could reduce the supply of vouchers by excluding from eligibility those drugs that were already widely available outside the United States (for example, drugs that had been available for a given indication for more than five years before FDA submission). Finally, Congress should require that manufacturers have a plan for ensuring drug access.

Conclusion

Congress and the FDA might find it easier to say "no" to expansions of the priority review voucher program if they used the evidence in this study about the impact of additional vouchers on the price of all vouchers. ∎

NOTES

1 Ridley DB, Grabowski HG, Moe JL. Developing drugs for developing countries. Health Aff (Millwood). 2006;25(2):313–24.

2 Gans JS, Ridley DB. Innovation incentives under transferable fast-track regulatory review. J Ind Econ. 2013;61(3):789–816.

3 Stefanakis R, Robertson AS, Ponder EL, Moree M. Analysis of neglected tropical disease drug and vaccine development pipelines to predict issuance of FDA priority review vouchers over the next decade. PLoS Negl Trop Dis. 2012;6(10):e1803.

4 Ridley DB. Priority review voucher [Internet]. Durham (NC): Duke University; 2016 Jan 8 [cited 2016 Mar 23]. Available from: http://priorityreviewvoucher.org

5 Berndt ER, Glennerster R, Kremer MR, Lee J, Levine R, Weizsäcker G, et al. Advance market commitments for vaccines against neglected diseases: estimating costs and effectiveness. Health Econ. 2007;16(5):491–511.

6 Towse A, Keuffel E, Kettler HE, Ridley DB. Drugs and vaccines for developing countries. In: Danzon PM, Nicholson S, editors. The Oxford handbook of the economics of the biopharmaceutical industry. New York (NY): Oxford University Press; 2012. p. 1–39.

7 Hensley S. Price rises for ticket to a quicker drug review by FDA. National Public Radio [serial on the Internet]. 2015 Aug 19 [cited 2016 Mar 23]. Available from: http://www.npr.org/sections/health-shots/2015/08/19/432887081/price-rises-for-ticket-to-a-quicker-drug-review-by-fda

8 Noor W. Placing value on FDA's priority review vouchers. In Vivo. 2009;27(8):1–8.

9 Matheny J, Smith B, Courtney B, Mair M. Drug and vaccine development for infectious diseases: the value of priority review vouchers. Clin Pharmacol Ther. 2009;85(6):571–2.

10 Robertson AS, Stefanakis R, Josepn D, Moree M. The impact of the US priority review voucher on private-sector investment in global health research and development. PLoS Negl Trop Dis. 2012;6(8):e1750.

11 Ridley DB, Sánchez AC. Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases. Lancet. 2010;376(9744):922–7.

12 Régnier SA, Ridley DB. Market watch: forecasting market share in the US pharmaceutical market. Nat Rev Drug Discov. 2015;14(9):594–5.

13 Grabowski HG, Ridley DB, Moe JL. Priority review vouchers to encourage innovation for neglected diseases. In: Eggleston K, editor. Prescribing cultures and pharmaceutical policy in the Asia-Pacific. Washington (DC): Brookings Institution Press; 2009. p 347–65.

14 Jenkins JK. CDER new drug review: 2012 update [Internet]. Silver Spring (MD): Food and Drug Administration; [cited 2016 Mar 23]. Available from: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM331454.pdf

15 Matheny J, Mair M, Smith B. Cost/success projections for US biodefense countermeasure development. Nat Biotechnol. 2008;26(9):981–3.

16 SDI Health is now part of IMS Health. For information about the National Prescription Audit, see IMS Institute for Healthcare Informatics. National Prescription Audit [Internet]. Collegeville (PA): IMS Health; [cited 2016 Mar 23]. (HRSN Data Brief). Available from: http://www.imshealth.com/files/web/IMSH%20Institute/NPA_Data_Brief-.pdf

17 Berndt ER, Nass D, Kleinrock M, Aitken M. Decline in economic returns from new drugs raises questions about sustaining innovations. Health Aff (Millwood). 2015;34(2):245–52.

18 To access the Appendix, click on the Appendix link in the box to the right of the article online.

19 DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. J Health Econ. 2016;47:20–33.

20 Mintz J, Chen D (University of Calgary, AB). The U.S. corporate effective tax rate: myth and the fact [Internet]. Washington (DC): Tax Foundation; 2014 Feb [cited 2016 Mar 23]. (Special Report No. 214). Available from: http://taxfoundation.org/sites/taxfoundation.org/files/docs/SR214.pdf

21 Grabowski HG, Ridley DB, Schulman KA. Entry and competition in generic biologics. Manage Decis Econ. 2007;28(4–5):439–51.

22 Winslow R, Walker J. Drug firms buy $67.5 million voucher to speed FDA review. Wall Street Journal. 2014 Jul 30.

23 Grabowski HG, Long G, Mortimer R. Recent trends in brand-name and generic drug competition. J Med Econ. 2014;17(3):207–14.

24 Huet N. Sanofi cholesterol drug touted as potential $3 billion blockbuster. Reuters [serial on the Internet]. 2013 Sep 25 [cited 2016 Mar 29]. Available from: http://www.reuters.com/article/us-sanofi-cholesterol-idUSBRE98O0SX20130925

25 Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010;9(3):203–14.

26 Adams CP, Brantner VV. Estimating the cost of new drug development: is it really $802 million? Health Aff (Millwood). 2006;25(2):420–8.

27 Kesselheim AS, Maggs LR, Sarpatwari A. Experience with the priority review voucher program for drug development. JAMA. 2015;314(16):1687–8.

28 Kesselheim AS. Priority review vouchers: an inefficient and dangerous way to promote neglected-disease drug development. Clin Pharmacol Ther. 2009;85(6):573–5.

29 Sonderholm J. In defence of priority review vouchers. Bioethics. 2009;23(7):413–20.

30 Grabowski HG, DiMasi JA, Long G. The roles of patents and research and development incentives in biopharmaceutical innovation. Health Aff (Millwood). 2015;34(2):302–10.