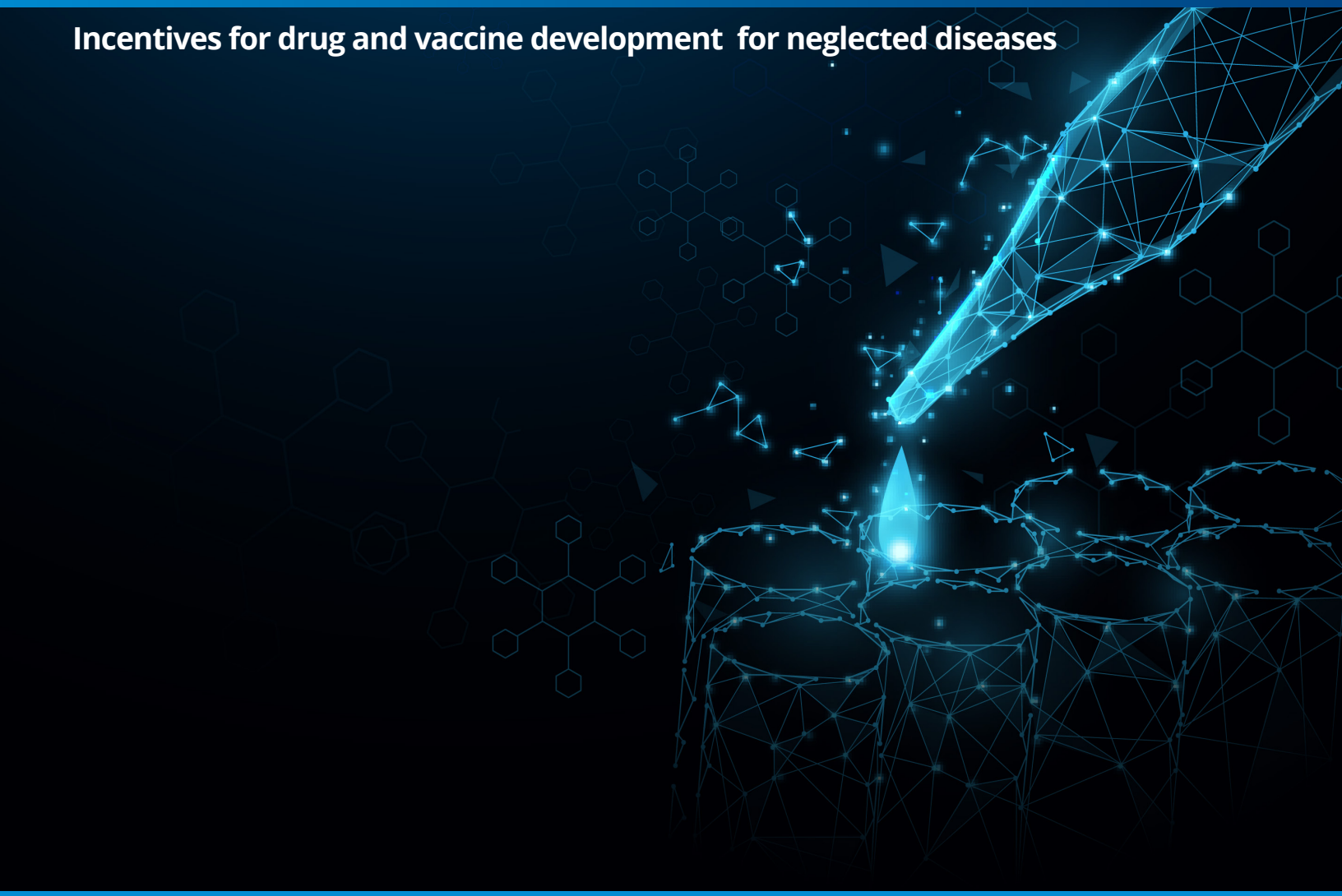
Design of a Transferable Exclusivity Voucher Program

Incentives for drug and vaccine development for neglected diseases



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Background

Developing a drug or vaccine is typically unprofitable when the people in need live in lower-income countries. For this reason, the drug industry neglects many infectious diseases. Drug development is also unprofitable when the existing market is limited and the interventions are aimed to address future risk, such as bioterror attacks, infectious disease pandemics, or antibiotic-resistant pathogens. The lack of commercial incentive discourages companies from investing in drug development for such diseases.

Governments and foundations have created incentives for drug and vaccine development for otherwise neglected diseases. The incentives fall into two categories: pull mechanisms and push mechanisms.

Pull mechanisms provide a known return on investment, a viable market, or reward for successful development and launch. There are at least four types of pull mechanisms. First, an advanced market commitment gives a successful developer a guaranteed purchase price for a given volume. Second, a market entry reward gives a successful developer a lump sum payment upon approval. Third, an extended exclusivity period gives a successful developer more time with limited competition. Fourth, a priority review voucher gives a successful developer a tradeable right to faster regulatory review.[1]

Push mechanisms provide up-front support to drug developers to reduce their costs and foster innovation. Examples of a push mechanism are a tax credit, such as through the Orphan Drug Act, or direct funding through grants and contracts, such as funding from the US National Institutes of Health (NIH). For example, the NIH and the Bill & Melinda Gates Foundation spent a combined $300 million on push funding for malaria in 2019.[2] The combined investment of all other governments and foundations totaled approximately $200 million of push funding for malaria that same year. The FDA's Tropical Disease Priority Review Voucher program offers a pull mechanism worth about $100 million for a new malaria drug (or drug for other eligible neglected diseases).[3] Yet, the need for investment is far greater as successful development of a new drug costs more than $1 billion dollars.[4,5]

We need another powerful incentive to ignite drug development for neglected diseases. One option for policy makers is to enact a transferable exclusivity voucher program. Exclusivity vouchers have been discussed at least since at least 2000,[6] refined in 2016,[7] and proposed by the U.S Congress in the "Re-Valuing Antimicrobial Products Act of 2018."[8] However, the exclusivity voucher program has yet to become law. In this paper, we describe the voucher program, detail four concerns raised about it, discuss how to address those concerns, and propose how to implement the program.

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Overview of the Transferable Exclusivity Voucher Program

The transferable exclusivity voucher ("the voucher" or "the voucher program") is a pull mechanism, in that offers drug manufacturers a reward after the approval of a product by the Food and Drug Administration (FDA). The way the voucher program works is that the U.S. government would grant a voucher to the developer of a new, approved product for a pre-defined, neglected disease. The voucher would extend marketing exclusivity for a different product. The developer could use the voucher to extend one of its own products or could sell the voucher to another drug developer for their use. (A detailed description of voucher selling appears later in the paper.)

Two drugs would be involved with each voucher:

1. The drug for which the developer receives the reward and
2. The drug for which the developer receives extended exclusivity.

The rationale for this approach is that the first product, for example a malaria drug, is likely not profitable. Therefore, extending its exclusivity would not provide a meaningful reward. Instead, the extended exclusivity is transferred to a different, more profitable product, such as a diabetes drug.

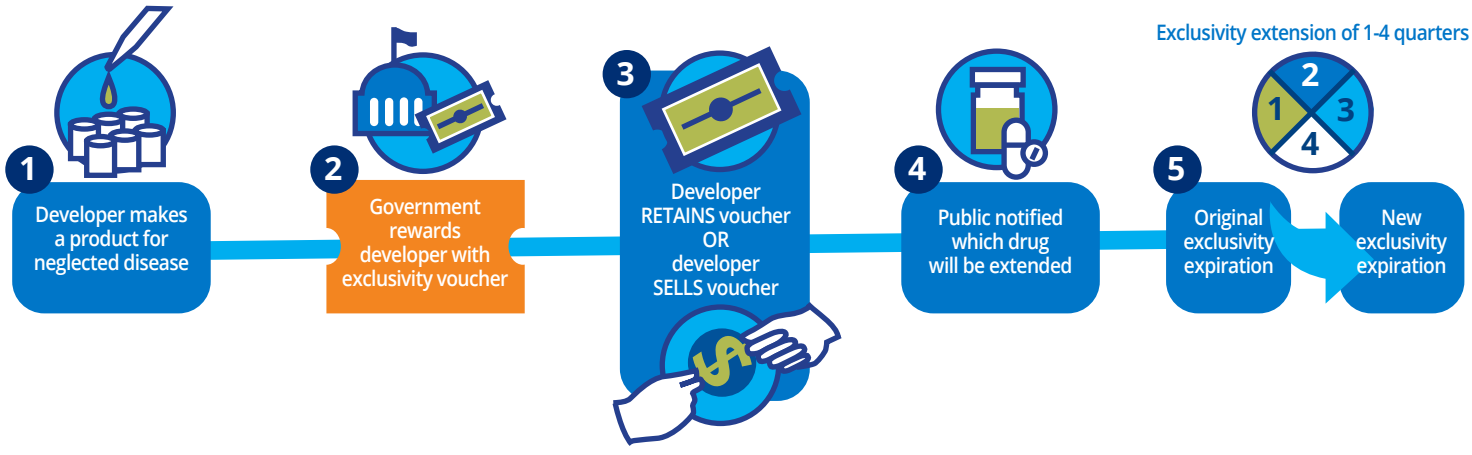
Previous exclusivity extensions have been politically viable, suggesting that an exclusivity voucher program could work too. The Pediatric Exclusivity Provision (1997) gives six additional months of exclusivity for a drug tested in children. The Generating Antibiotic Incentives Now (GAIN) Act (2012) gives five additional years of exclusivity for certain antibiotics. However, the GAIN Act is limited in its power as an incentive because it applies to a drug that likely has low revenue, and the benefit accrues years in the future when the new drug faces generic competition. For example, if the GAIN Act extends exclusivity of a $100 million per year drug beginning 10 years following market entry, it has little present value. In contrast, a transferable exclusivity voucher could be applied to a multi-billion-dollar drug beginning two years after receiving the voucher.

The process for receiving and using the voucher would be as follows **(Figure 1)**:

1. A drug developer makes a product for a neglected disease and submits for FDA approval;
2. FDA gives a voucher to the drug developer as a reward for successful development of a product that meets the pre-defined eligibility criteria and the creation of an accompanying access plan;
3. The drug developer would determine whether to use the voucher itself or sell it to another company;
4. The voucher user (either the drug developer or the voucher buyer) would notify the public of the drug it intends to use the voucher on at least a year before using it to allow generic drug makers to adjust production schedules and allow insurers to account for the exclusivity extension in setting insurance premiums*;
5. After expiration of other exclusivities, the voucher user would extend the exclusivity for the selected product.

**The voucher user could change plans and transfer the announcement to a different drug but changing would restart the one-year notification clock.*

FIGURE 1 | **Process for Use of a Transferable Exclusivity Voucher**



Company Financial Considerations

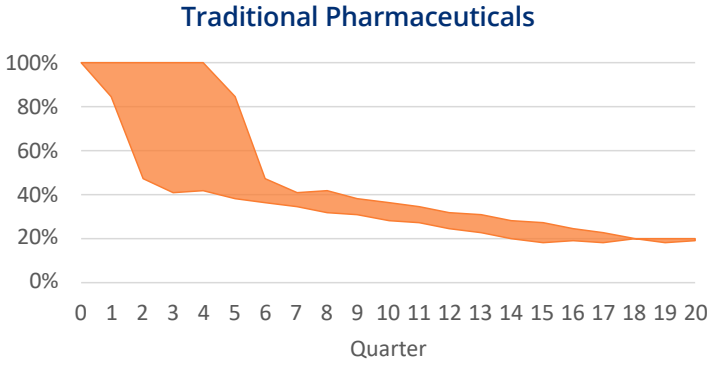
Additional Revenue

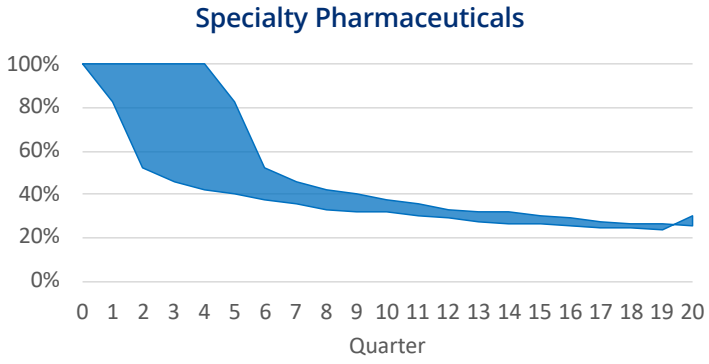
A voucher used to extend exclusivity for a profitable drug could provide significant returns and a strong incentive for companies. To understand the potential financial returns from a voucher program, we estimated the added profit from an additional year of exclusivity. First, we estimated the sales erosion for an originator company over five years when its product loses exclusivity. Second, we estimated the increased revenue if generic or biosimilar entry was delayed by one year. We used the sales erosion curve for the originator and then shifted the curve over by one year to plot the effect of a year of extended exclusivity on the originator's sales over time **(Figure 2)**. The shaded area between the two curves shows the gains to the originator company from the delay. For simplicity, we illustrated a one-year extension, but as discussed below, we propose that some extensions would be shorter.

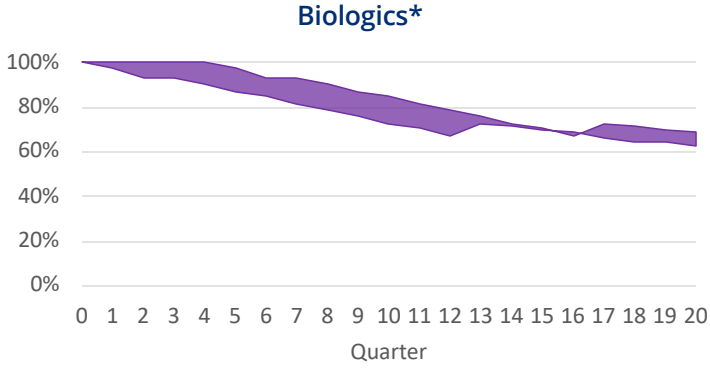
The value of an additional year of exclusivity is less than the annual revenue for the selected product for two reasons. First, annual revenue does not immediately fall to zero following exclusivity. We estimate that extending exclusivity by a year would generate an additional 42 percent of the pre-exclusivity revenue in terms of present value. (We calculate the present value because money promised in the future is worth less today. We calculate present value using a discount rate of 10.5 percent as in previous studies.[4,5]) Second, not all of pharmaceutical sales accrue to the drug developer. Others in the supply chain, such as insurers, pharmacy benefit managers, retailers, and wholesalers, capture some revenue, with the drug developer capturing 58 percent on average.[9] Multiplying 42 percent and 58 percent gives an additional 25 percent for the drug developer from extending exclusivity by a year. For example, the value of a one-year extension for a drug with $1 billion in revenue would be about $250 million.

While pharmaceutical sales erode rapidly after patent expiration, the erosion is more gradual for biologics **(Figure 2)**. Our analysis is based on biologics through June 2020, but the biosimilar market is evolving rapidly. We expect that over time the biologics erosion curves will look increasingly like the pharmaceutical erosion curves. A more competitive biosimilar market would make the voucher program more attractive to companies and, therefore, create a stronger incentive for developers. See Appendix for more details on this analysis.

FIGURE 2 **Additional Quarterly Revenue Received by Originator Company Due to an Extra Year of Exclusivity**







** based on past sales of biologics and biosimilars through June 2020*

Cost of Drug Development and Access

We estimate that the target value of the voucher reward should be about $1.5 billion. We chose this target to cover development and access costs. According to a study of clinical trial costs, the mean cost was about $1.3 billion per successful product in the 2010s.[5] The estimate accounts for failures and opportunity cost. The $1.3 billion is less than the estimate from the Tufts study[4], in part because the Tufts study included pre-clinical costs, such as basic science and animal studies. If the voucher is intended to motivate drug developers to invest in basic science to find new targets and test them in animals, then the prize would need to be larger. At this value, we are assuming that push mechanisms, such as grants from NIH and foundations, can fund pre-clinical costs. We target $1.5 billion (rather than $1.3 billion) to account for some of the access costs and clinical trial cost inflation.

A drug developer's costs are not complete after the drug reaches the market. Introducing a new medicine in low- and middle-income countries can be a difficult and resource-intensive process. For instance, there can be lengthy delays in regulatory approvals and additional steps may be needed for pre-qualification by the World Health Organization (WHO), approval on formularies, or inclusion in local clinical guidelines. Additional investment in clinician training or diagnostic tools also may be needed. For some companies, these challenges and risks are a disincentive to making the efforts to ensure access in those settings. The burden of going through the regulatory and market registration process for multiple countries with a small potential market can discourage companies from broadly introducing a new medicine. The voucher reward must consider the costs and barriers for delivering a product and ensuring access if development of an access plan for the product is to be a requirement of the program. To be an effective incentive, the voucher must adequately reward the drug developer beyond costs of research and development (more on value of the reward in the next section).

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Addressing Concerns about the Voucher Program

A transferable exclusivity voucher valued at more than $1 billion dollars could be a powerful incentive to encourage drug development for neglected diseases. However, there are four concerns about the voucher program:

1. extending exclusivity can create a cost burden for U.S. patients and payers;
2. the program could excessively reward drugs developers;
3. the voucher-receiving product might be insufficiently novel;
4. the voucher-receiving product might not reach patients.

In the following section, we explore these concerns and then propose ways to mitigate them to help people from other countries who would benefit from a malaria drug.

CONCERN 1
Cost Burden for Patients and Payers

Recall that there are two drugs for each voucher. For example, the developer of a malaria drug wins the voucher, and the manufacturer of a cholesterol drug uses the voucher for longer exclusivity. Here we examine the cost burden to the patients using a cholesterol drug with extended exclusivity. Extending exclusivity for a product delays generic and biosimilar competition. As a result, patients and payers in the U.S. must wait longer for lower prices. This can lead to higher spending.[10] Also, it might be considered unfair to delay competition in the U.S. for the cholesterol drug to help people from other countries who would benefit from a malaria drug.

RESPONSE TO CONCERN 1:
Patient Out-of-Pocket Costs are Limited

We estimated the effect of an exclusivity extension on U.S. patients and payers. To do this, we examined out-of-pocket drug spending by patients covered by Medicare, Medicaid, or commercial insurance. We also estimated how much savings generic or biosimilar competition generates across different product types (traditional pharmaceuticals, specialty pharmaceuticals, and biosimilars).

For the analysis we selected seven top-earning drugs using 2018 claims data from IQVIA **(Table 1)**. IQVIA is one of the world's leading sources of pharmaceutical industry data. We selected these seven drugs because each was in the top 25 in total spending, each had patent expiration in 2024 or later, and together they represent a variety of therapeutic and reimbursement types.

We found that most costs for these drugs are borne by payers. Patients pay only a small percentage of total drug costs, particularly for the drugs with high annual costs **(Table 1)**. We also determined that the savings for patients due to generic and biosimilar competition are minimal in the first year. Most insured patients are protected by annual out-of-pocket spending limits. Due to the high price of most top-selling drugs, the patient is likely to reach their annual out-of-pocket spending limit. Even after the first year of competition, prices are still likely to be high enough that a patient would meet their out-of-pocket limit, therefore savings to the patient are limited. Savings are more limited for biosimilar competition (estimated $20 in annual savings for patients) than for traditional pharmaceuticals, but this could change as the biosimilar market evolves. See **Appendix** for more details on this analysis.

Little of the cost of extended exclusivity would be paid by the patient taking the drug. Most of the cost will be paid by the payer. The payer will spread the cost among all insured patients as a higher health insurance premium. If the voucher program increased drug spending by $2 billion in a year, we estimate that for a family paying $10,000 in health insurance premiums, the premium would increase by $5. So, the cost of exclusivity is paid in slightly increased insurance premiums across all members. In this way, it is like a tax that is broadly distributed.

Uninsured patients generally do not pay for the top-selling drugs. They will often receive older, cheaper treatment options or they will receive the expensive drug through a drug developer's patient assistance program. Extended exclusivity of a top-selling drug would not increase spending for uninsured patients but may delay their access to a cheaper generic or biosimilar version of the new drug. To protect uninsured patients, policymakers may consider steps, such as requiring the brand name manufacturer to provide coupons and patient assistance programs.

Regarding the fairness of one group paying more to help another, this is the nature of health care. People pay higher taxes and insurance premiums to help those who are ill. Furthermore, the voucher program is intended to address infectious diseases. Protecting a stranger from an infectious disease could benefit you if the stranger is less likely to transmit the disease after being treated or vaccinated. Furthermore, the U.S. has a long-standing history of using taxpayer dollars to address global health needs with broad political support.

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TABLE 1 Average Annual Cost and Average Share of Spending by Patients by Insurance Type

Reimbursement	Product	Annual Cost	Share of Annual Cost Paid by Patients		
			Commercial	Medicare	Medicaid
Medical	Pembrolizumab (Keytruda)	$172,890	2%	1%	0%
	Nivolumab (Opdivo)	$180,024	2%	2%	0%
Pharmacy, Specialty	Etanercept (Enbrel)	$81,354	1%	2%	0%
	Elvitegravir (Genvoya)	$40,020	2%	1%	0%
Pharmacy, Traditional	Lurasidone (Latuda)	$16,413	4%	1%	0%
	Dulaglutide (Trulicity)	$10,946	5%	7%	0%
	Rivaroxaban (Xarelto)	$6,000	9%	13%	1%

CONCERN 2
Unneeded Rewards for Drug Developers

The voucher program could provide a greater reward to drug developers than necessary in two ways:

1. a voucher recipient might receive a voucher worth more than it invested in drug development and access;
2. if the voucher is sold, the buyer might receive much more benefit from using the voucher than what it paid.

RESPONSE TO CONCERN 2:
Adjust the Length of Exclusivity

We recommend adjusting the exclusivity duration based on the expected number of quarters needed to achieve a target reward. Recall that we assume the value of an extension for a drug developer is about 25 percent of its annual sales. The 25 percent takes into account the 42 percent in added sales based on the erosion analysis and the 58 percent that the drug developer (rather than intermediaries) retains.[9] Yet, a drug with high sales and/or a long extension could still exceed the target reward of $1.5 billion.

For example, the drug Eliquis had about $8 billion in U.S. sales in 2020. If the value to the drug developer of an additional year of exclusivity is 25 percent of that amount, then the value would be $2 billion. If, rather than a year of extra exclusivity, the drug was given only two quarters of extra exclusivity, then the value of the extension would be $1 billion.

We recommend using tiers based on a drug's U.S. sales in the previous year to determine the number of quarters of additional exclusivity granted by the voucher. In our proposed tiers, drugs with annual sales of less than $6 billion would receive four quarters of additional exclusivity. Again, assuming the voucher is worth 25 percent of annual sales to the drug developer, the voucher would be worth up to $1.5 billion. Tiers 2 and 3 are also set to a maximum value of $1.5 billion **(Table 2)**.

For drugs with annual sales of $12 billion or greater, we recommend one quarter of extended exclusivity. This voucher would be worth only $750 million for drugs at the low end of the range but would be worth more at higher annual sales.

The tiers have four advantages. First, tiers limit excess profit. In 2020, only Humira had sales in the U.S. over $12 billion **(Table 3)**. Based on the tiers, Humira would receive only one quarter of additional exclusivity. In this scenario, Humira would earn an additional $1 billion in the additional quarter.

TABLE 2 | **Tiered Variable Exclusivity Extension Based on Annual Sales Revenue**

Tier	Annual sales in previous year (millions)	Additional exclusivity (quarters)	Added revenue to developer (millions)
1	> $12,000	1	> $750
2	$8,000 - $11,999	2	$1,000 - $1,500
3	$6,000 - $7,999	3	$1,125 - $1,500
4	< $6,000	4	< $1,500

Second, tiers induce multiple bidders for the voucher, thus increasing the value for the developer. For example, a company with a product with an annual revenue of $7 billion might have the same bid as a company with a product with an annual revenue of $10.5 billion, because both can receive an additional $1.3 billion in value from exclusivity **(Table 2)**.

Third, using tiers (rather than share of sales) allows the extension to be dependent on sales without knowing precise sales. For example, whether the company revenue was $6.5 billion or $7.5 billion, the company will receive three quarters of additional exclusivity.

Fourth, the tiers could motivate a drug developer to lower its price to fall within a tier to gain greater exclusivity in the future.

TABLE 3 | Top 10 Drugs by Sales in 2020

Drug Name	Product Type	Manufacturer(s)	2020 US Sales (millions)	Indication
1.Humira (adalimumab)	Biologic	AbbVie	$16,112	rheumatoid and psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis
2. Keytruda (pembrolizumab)	Biologic	Merck	$8,352	various cancers
3. Eliquis (apixaban)	Pharmaceutical	Bristol Myers Squibb and Pfizer	$8,173	blood clots
4. Revlimid (lenalidomide)	Biologic	Bristol Myers Squibb	$8,291	myelodysplastic syndrome, multiple myeloma, and mantle cell lymphoma
5. Eylea (aflibercept)	Biologic	Regeneron Pharmaceuticals (US) and Bayer (outside of US)	$4,950	age-related macular degeneration, macular edema, and diabetic retinopathy
6. Imbruvica (ibrutinib)	Pharmaceutical	Pharmacyclics (AbbVie) and Janssen (Johnson & Johnson)	$6,126	chronic lymphocytic leukemia/small lymphocytic lymphoma with 17p deletion, and Waldenström's macroglobulinemia
7. Dupixent (dupilumab)	Biologic	Sanofi Genzyme and Regeneron Pharmaceuticals	$6,674	atopic dermatitis, asthma, chronic rhinosinitus with nasal polyps
8. Stelara (ustekinumab)	Biologic	Janssen (Johnson & Johnson)	$5,240	plaque psoriasis and psoriatic arthritis
9. Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide)	Pharmaceutical	Gilead Sciences	$6,095	HIV
10. Opdivo (nivolumab)	Biologic	Bristol Myers Squibb	$3,945	various forms of cancer

CONCERN 3
Insufficient Novelty for the Voucher Recipient

If the bar to gain a voucher was not sufficiently high, then companies could receive vouchers for drugs with only small improvements on existing therapies or for drugs already marketed in other countries. For example, Novartis received a priority review voucher for its malaria treatment, Coartem® (artemether/lumefantrine), which was already marketed in other countries.

RESPONSE TO CONCERN 3:
Rewarding Needed Innovation

To ensure that the voucher is rewarding high-quality, innovative products for neglected diseases, we recommend that the eligibility requirements include target product profiles.

A target product profile outlines the desired characteristics for the development of a product for a specific disease or set of diseases. The characteristics may include target population, temperature stability, route of administration, dosing frequency, cost, and clinical efficacy. Target product profiles are used by industry, funders, multilateral organizations, and non-profits to guide drug development. For example, WHO has target product profiles that focus on public health priorities.[11] Funders such as the Wellcome Trust, NIH,[12] the Bill & Melinda Gates Foundation, and Adjuvant Capital also create target product profiles for the research and development projects they fund. The Drugs for Neglected Diseases Initiative (DNDi), a non-profit organization, has developed its own target product profiles for several neglected tropical diseases with descriptions of both ideal and acceptable characteristics.[13]

The voucher program should develop target product profiles specific to the innovation needs of affected populations. This means a drug would need to meet the criteria in the target product profile for the disease to be eligible for the voucher.

We recommend that an advisory committee develop the target product profiles before the start of the voucher program. The target product profiles can draw from existing ones developed by other stakeholders and should be informed by patient perspectives and the needs of lower-income countries. Consider the example in **Table 4**.

The voucher program should develop target product profiles specific to the innovation needs of affected populations.

A drug would need to meet the criteria in the target product profile for the disease to be eligible for the voucher.

TABLE 4 **Target product profile for sleeping sickness (human African trypanosomiasis) developed by Drugs for Neglected Diseases initiative[14]**

Product Targets	Ideal Result	Acceptable Result
Target population	Effective against stages 1 and 2 Effective in melarsoprol refractory patients All patients, including pregnant and lactating women	Effective against stages 1 and 2
Target species	Efficacy against both *T.b. gambiense* and *T.b. rhodesiense*	Efficacy against *T.b. gambiense* only
Efficacy	Effective in melarsoprol refractory patients	Clinical efficacy > 95% at 18-month follow-up
Safety/tolerability	<0.1% drug related mortality No monitoring for adverse events (AEs)	<1% possibly related mortality Weekly simple lab testing (field testing) for AEs
Formulation	Adult and paediatric formulations	
Treatment regimen	<7 days oral once daily or <7 days intramuscular injection once daily	Weekly simple lab testing (field testing) for AEs
Stability	Stability in climatic zone 4 for >3 years	Stability in climatic zone 4 for > 12 months
Cost	< EUR 30 / course (drug cost only)	< EUR 100 / course < EUR 200 / course OK if very good on other criteria

After the target product profiles are developed, FDA would be responsible for reviewing products submitted to the voucher program to ensure they meet the minimum acceptable characteristics. The FDA would incorporate this review into their regulatory review process for the drug. We recommend that Congress create an additional user fee to cover the additional effort needed for the review.[3]

CONCERN 4
Ensuring Access to Rewarded Product

The voucher program will be successful only if people who need the drugs can use them. For example, the drug miltefosine for leishmaniasis received a priority review voucher, but advocacy groups have argued that the price is too high for people in low-income countries.[15] WHO defines patient access as "having medicines continuously available and affordable at public or private health facilities or medicine outlets that are within one hour's walk from the homes of the population."[3,16]

RESPONSE TO CONCERN 4:
Planning for Access

To address concerns about access, particularly for low- and middle-income countries, the voucher program should require that the drug developer submit an access plan for the product. Fortunately, some companies are already doing this. About half of companies assessed in the 2021 Access to Medicine Index report systematically planning for access to their products during development.[17] This requirement would motivate more companies to do so.

The voucher program should require a company to submit an access plan to be considered for the voucher and these access plans should be made publicly available on FDA's website. FDA should provide a guide prior to the start of the program to support the development of these access plans and to set standards. The guide could be drawn from or modeled on existing resources, including the Stewardship and Access Plan Guide developed by CARB-X[18] and access plans created for product development partnerships, such as DNDi.

We recommend the creation of a second advisory committee. The first advisory committee will create the target product profiles. The second will create the access planning guide and should be comprised of global experts on access to medicine, including those who will monitor the access plans and hold developers accountable.

Creating a guide ensures that developers are considering all the necessary components of access as defined by stakeholders. There are several core principles for access plans that should be considered in the guide, including country registrations, affordable pricing strategies, licensing considerations, planning for manufacturing and supply, education and capacity building considerations, and product stewardship **(Table 5)**.

TABLE 5 | **Principles for Access Planning**

Registration	The developer should prioritize and plan for product registration in countries with greatest need based on disease burden. Developers should consider applying for WHO prequalification, using accelerated registration mechanisms, or coordinating with multilateral procurers such as GAVI for vaccines or the Global Fund for tuberculosis and malaria products.
Affordability	The developer should commit to affordable prices in low- and middle-income countries. The price should be informed by ability to pay, value, and the cost of goods and operations. A developer should explore a range of affordable pricing options, including cost plus and value and equity pricing. We expect that the developer will need only a low margin given the value of the voucher.
Licensing	The developer should consider voluntary licensing and technology transfers to third parties to facilitate broader local access. The developer might also agree not to enforce patents in low-income countries.
Manufacturing and supply	The developer should plan ahead for low-cost manufacturing where possible and consider local manufacturing commitments. It may also plan for shortage mitigation strategies and supply forecasting.
Education and/or capacity building	In some cases, training for healthcare workers may be needed. The developer should consider provider education or training in the access plans. Further, the developer should consider the country contexts where the product will be launched and whether capacity building efforts should be conducted in partnership with other organizations.
Stewardship	The developer should consider proper packaging and product information for the product to ensure safety and appropriate use. For new antimicrobials, developers may also consider education on appropriate use, resistance surveillance programs, responsible manufacturing practices, and susceptibility tests and diagnostics.

Monitoring Access Plans

After the access plans are made publicly available, global health organizations and advocates can hold developers accountable to the plans. Advocacy groups such as Médecins Sans Frontières (MSF) and Knowledge Ecology International have experience in holding pharmaceutical companies accountable through public campaigns. Other organizations such as the Access to Medicine Foundation have experience tracking companies' progress on upholding their public commitments.

In addition to holding developers publicly accountable, we recommend that the U.S. Government Accountability Office evaluate the program every five years, including progress on implementing access plans. If developers do not follow through on their access plans, lawmakers could consider introducing civil money penalties for future developers that fail to show progress on ensuring access.

Improving Collaboration between the FDA and WHO

To facilitate access to essential medicines in low- and middle-income countries, the European Medicines Agency (EMA) has a procedure called EU-M4all, previously known as Article 58.[19] In the procedure, EMA evaluates the medicine in collaboration with WHO and relevant non-European Union authorities, in the context of its use in the target population. The goal is to facilitate the granting of a national marketing authorization or the registration of a medicine at national or regional level. There is no equivalent program in the U.S. The creation of a procedure in the U.S. similar to the EU-M4all procedure could strengthen the voucher program by providing a clearer pathway for developers to ensure access to their product. This mechanism also would help other programs that encourage drug development for neglected diseases, such as the priority review voucher program.

Selling a Voucher

The voucher recipient has the option to use the voucher for one of its products or sell the voucher to another company. If the voucher recipient is a larger company with lucrative commercial products to extend, then the voucher is more valuable used than sold, due to U.S. taxes. If the voucher recipient is a smaller company or a non-profit drug developer that does not have lucrative commercial products to extend, then it is more valuable sold.

Allowing the voucher to be sold expands the pool of drug developers. A non-profit company might not have use for a voucher on its own. It could develop a drug and then sell the voucher to a company with a portfolio of commercial drugs. For example, Medicines Development for Global Health, a non-profit company in Australia, received a priority review voucher for its river blindness drug. The potential to sell a voucher would motivate investment by the non-profit company and provide resources to promote access.

The sale of a voucher may work in this way for a hypothetical, small company. The small company has two large companies bidding for a voucher. One large company has a drug with $8.4 billion in annual sales while the other has a drug with $5 billion in annual sales. Both expect generic competition in three or four years. The company with annual sales of $8.4 billion would get two quarters of exclusivity, valued at $1.05 billion (8.4 multiplied by half a year multiplied by 25 percent). The company with annual sales of $5 billion would get four quarters of exclusivity, valued at $1.25 billion (five multiplied by a full year multiplied by 25 percent). Both companies probably would bid around $1 billion, but presumably the latter company would bid slightly higher.

A company might hold a voucher for a few years. A small company might hold a voucher while waiting for a higher bid. A large company might hold a voucher while waiting for a commercial drug to complete testing. But there is a time value of money, meaning a company would generally rather make a dollar today than a dollar in the future. Therefore, it is unlikely that a company would hold the voucher for an extended period of time.

Management of the Exclusivity Voucher Program

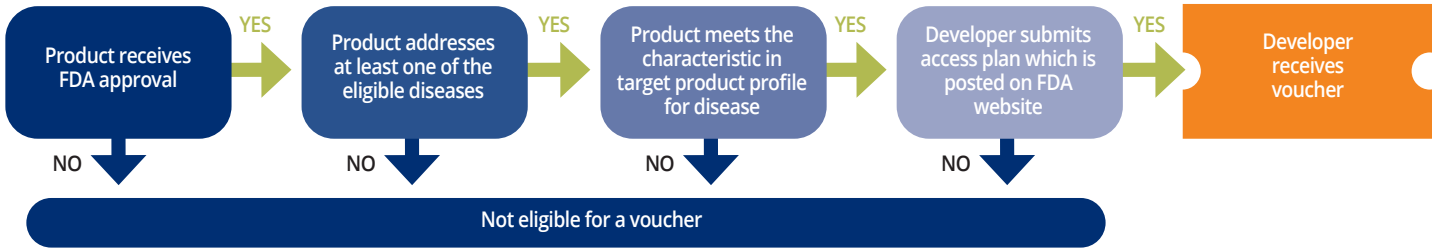
We propose that the FDA administer the voucher program as the agency already has experience managing the priority review voucher program. The FDA will have at least four responsibilities in managing the exclusivity voucher program:

- host an advisory committee to determine the target product profiles;
- host an advisory committee to develop access plan guidance;
- compare drug submissions to the target product profile and determine eligibility; and
- collect and publicly post access plans.

The advisory committees could be similar to those hosted by the U.S. Department of Health and Human Services, such as the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. We defer to the FDA on how best to establish these committees and note that one option would be to give the FDA Office of Global Policy and Strategy responsibility for creating them.

The additional review of target product profiles and collecting of access plans will require additional time and resources for the FDA from Congress. We recommend that the eligibility review for the voucher take place after regulatory approval. The voucher eligibility review and decision should be made within a specified timeframe (e.g., three months), following approval. This order of events will prevent the additional review from slowing market entry of the product.

FIGURE 3 FDA Process for Determining Voucher Eligibility



Program Budget

We propose that Congress enable the FDA to charge a voucher user fee to cover the costs of administering the program. The user fee would be in addition to the standard regulatory review fee paid by drug developers to the FDA. The voucher user fee would be equal to the current review fee, so a potential voucher recipient's FDA total review fee would be doubled. Initially, Congress will need to allocate startup funding for the program of up to $5 million. This amount reflects the estimated budget needed to convene the two advisory committees – one to develop target product profiles and another to develop access plan guidelines.

One Voucher per Drug

If an overlap exists between diseases eligible for an exclusivity voucher and a priority review voucher, we recommend that the developer receive only one of the two for its product. If a drug or vaccine is eligible for both, then we recommend that the exclusivity voucher be the default program. The manufacturer would have the option to switch to the priority review voucher upon request. For example, a company that develops a malaria vaccine would be given an exclusivity voucher but not a priority review voucher. While we recommend a limit on voucher recipients, we do not recommend a limit on the use of vouchers. For example, a company could use a priority review voucher for faster review at launch of a diabetes drug, and a decade or so later could use an exclusivity voucher for longer exclusivity for the diabetes drug.

Diseases Eligible for the Voucher

The voucher program must specify a list of diseases that are eligible for the reward. We recommend three options for disease eligibility for vouchers based on areas of significant global public health need.

ELIGIBILITY OPTION 1 Neglected Infectious Diseases that Disproportionately Affect Lower-Income Countries

Diseases that primarily or disproportionately affect people in lower-income countries have too few available treatments. The countries with the greatest need for these products have a limited ability to pay for them, and therefore, do not offer an attractive market. Global health advocates have been calling for incentives to encourage and accelerate development of innovations for neglected diseases.

Some incentives already exist for neglected diseases that affect lower-income countries. The U.S. government funds research for these diseases through the National Institute of Allergy and Infectious Diseases. Also, in 2007 Congress created the Tropical Disease Priority Review Voucher Program as a reward for drug development. However, progress on drug development for these diseases is slow relative to the enormous need. For instance, by the end of 2020 only 12 drugs for tropical diseases had been awarded a priority review voucher.[3] More incentives are needed to address these research and development needs.

An exclusivity voucher program has the potential to offer a reward of greater than $1 billion to encourage increased investment in products for these diseases. One option for voucher eligibility is to reward development of medicines and vaccines that target neglected diseases that primarily impact lower-income countries.

The list of eligible diseases for Option 1 can be drawn from lists already developed by experts. For example, WHO's list of neglected tropical diseases identifies 20 infectious diseases that are endemic in tropical and subtropical regions and primarily affect populations living in poverty **(Table 6, column 1)**.[20] Policy Cures Research also has identified a list of neglected diseases and specific research needs for each in its G-FINDER report.[21] Like the original list of diseases for the Tropical Diseases Priority Review Voucher Program, the list of eligible diseases for the exclusivity voucher program might include a combination of WHO's neglected tropical diseases and other diseases, such as those identified by Policy Cures Research.

In **Table 6**, we propose a set of neglected diseases impacting lower-income countries for which the voucher might be rewarded. Policy Cures Research's list also includes hepatitis B, hepatitis C, and HIV, but we omitted them because they have a substantial market in high-income countries.

TABLE 6 Neglected Diseases Affecting Lower-Income Countries

Neglected Tropical Diseases from WHO[23]	Other Neglected Diseases
Buruli ulcer	Bacterial pneumonia *(S. pneumoniae)*
Chagas disease	Bacterial meningitis *(N. meningitidis)*
Dengue and chikungunya	Cryptococcal meningitis
Echinococcosis	Diarrheal diseases (cholera, rotavirus, shigella, giardiasis)
Elephantiasis (lymphatic filariasis)	Malaria
Foodborne trematodiases	Salmonella infections
Guinea worm disease	Tuberculosis
Leishmaniasis	
Leprosy	
Mycetoma	
Onchocerciasis (river blindness)	
Rabies	
Scabies	
Schistosomiasis	
Sleeping sickness	
Snake bite envenoming	
Soil-transmitted helminths (intestinal worms)	
Taeniasis and cysticercosis	
Trachoma	
Yaws	

ELIGIBILITY OPTION 2 Adding Antimicrobial Resistant Infections

A second option is to supplement the list of diseases in Option 1 with a set of diseases that also pose a risk to Americans. Antimicrobial resistance is a growing global threat. In the U.S. alone, more than 2.8 million antibiotic-resistant infections occur each year, and more than 35,000 people die as a result.[22] Globally, it is estimated that 700,000 people die each year from antimicrobial infections.[23]

New antibiotics are needed to treat bacterial infections that have developed resistance to commonly prescribed antibiotics. However, new antibiotics must be reserved and used sparingly when a patient does not respond to the first-line treatment. This means only limited quantities of the drug are needed, offering poor return on investment for drug developers.[23]

The global nature of the antimicrobial resistance crisis – affecting both poor and rich countries – has spurred efforts to address the need for new antibiotics. Several incentives (largely push incentives) already exist, and others are being considered by lawmakers (i.e., PASTEUR, REVAMP, and DISARM Acts). Including antimicrobial resistant infections in the list of diseases eligible for the exclusivity voucher could help garner political support for the program.

The U.S. Centers for Disease Control and Prevention (CDC) reports a list of 18 antibiotic-resistant infections which pose a threat.[25] The list primarily consists of bacterial infections but also includes several fungal infections. These 18 infections can be added to the list of eligible diseases in **Option 1 (Table 7).**

Antimicrobial resistance is a growing global threat.

Adding antimicrobial resistant infections to the list of eligible diseases has several advantages. First, it would more directly benefit Americans. Second, it would increase the number of advocacy groups supporting legislation to establish exclusivity vouchers. Third, if more vouchers were awarded, then it would help establish the voucher market more quickly.

TABLE 7 CDC's 2019 List of Antibiotic Resistance Threats[22]

Carbapenem-resistant *Acinetobacter*
Candida auris
Clostridioides difficile
Carbapenem-resistant Enterobacterales
Drug-resistant Neisseria *gonorrhoeae*
Drug-resistant *Campylobacter*
Drug-resistant *Candida*
ESBL-producing Enterobacterales
Vancomycin-resistant *Enterococci* (VRE)
Multidrug-resistant *Pseudomonas aeruginosa*
Drug-resistant nontyphoidal Salmonella
Drug-resistant *Salmonella* serotype Typhi
Drug-resistant *Shigella*
Methicillin-resistant *Staphylococcus aureus* (MRSA)
Drug-resistant Streptococcus pneumoniae
Drug-resistant Tuberculosis
Erythromycin-Resistant Group A *Streptococcus*
Clindamycin-Resistant Group B *Streptococcus*

New antibiotics are needed to treat bacterial infections that have developed resistance to commonly prescribed antibiotics.

ELIGIBILITY OPTION 3 Adding Emerging Infectious Diseases

A third option for the list of eligible diseases is to add emerging infectious diseases. The COVID-19 pandemic demonstrated the enormous damage an emerging disease can inflict. With COVID-19, there was incentive for rapid and significant investment in vaccines and therapeutics because high-income countries were severely impacted; this is not always the case. For example, the same sense of urgency in development did not occur for outbreaks of Ebola and Zika, which primarily affected lower-income countries and regions. An incentive, such as the voucher, could be beneficial for developing products to combat emerging infectious diseases that are designed for use in low-income countries.

Policy Cures Research also has developed a list of emerging infectious diseases with drug and vaccine development needs in its G-FINDER report.[24] This list can be found in **Table 8**. We retained the G-FINDER list, although we believe that some coronavirus diseases have sufficient commercial incentive and should not be eligible. Also, chikungunya already appears in **Option 1 (Table 6)**.

Emerging infectious diseases could be added to the lists in **Option 1** or **Option 2**. Similar to **Option 2**, the broader set of diseases, including some which may pose a global threat, could help garner more support from advocates and lawmakers. As with other incentive programs, diseases can be added to the list as new threats emerge.

TABLE 8 Emerging Infectious Diseases Based on G-FINDER[24]

Arenaviral haemorrhagic fevers
Lassa fever
Other arenaviral R&D in combination with Lassa fever
Arenaviral haemorrhagic fevers other than Lassa fever
Bunyaviral diseases
Crimean-Congo Haemorrhagic Fever (CCHF)
Rift Valley Fever (RVF)
Severe Fever with Thrombocytopenia Syndrome (SFTS)
Other bunyaviral R&D in combination with CCHF and/or RVF
Bunyaviral diseases other than CCHF, RVF and SFTS
Chikungunya
Coronaviral diseases
Middle East Respiratory Syndrome (MERS)
Severe Acute Respiratory Syndrome (SARS)
Coronavirus disease 2019 (COVID-19)
Other coronaviral R&D in combination with MERS and/or SARS and/or COVID-19
Highly pathogenic coronaviral diseases other than MERS, SARS and COVID-19
Emergent non-polio enteroviruses (including EV71, D68)
Filoviral diseases
Ebola
Marburg
Other filoviral R&D in combination with Ebola and/or Marburg
Filoviral diseases other than Ebola and Marburg
Henipaviral diseases
Nipah
Other henipaviral R&D including in combination with Nipah
Henipaviral diseases other than Nipah
Zika

Conclusion

For diseases that have the greatest burden in lower-income countries, a significant need exists for new medicines and vaccines. Yet, there is a lack of commercial incentive for such products. The same is true for new anti-infectives for resistant pathogens. The exclusivity voucher program we propose meets this need by offering a reward large enough to recoup costs of research and development, without requiring direct appropriations from the government. Further, the voucher program described here offers ways to address four major concerns from stakeholders.

With a broad list of eligible diseases, including threats to people living in the U.S., the voucher could attract the necessary political support for implementation. If enacted, the voucher program has the potential to make a meaningful impact on drug development for neglected and other diseases.

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Appendix

Supporting Analysis for 'Additional Revenue'

Methods

We calculated how spending erodes due to competition from biosimilars and generics. We estimated the financial returns that drug developers would earn if generic or biosimilar entry were delayed by one year. We assumed that 58 percent of the revenue went to the drug developer.[7] The remaining 42 percent went to others in the supply chain, including insurers, pharmacy benefit managers, retailers, and wholesalers as fees, markups, and rebates.

We also calculated the present value of the extra revenue that pharmaceuticals and biologics earned from delaying generic or biosimilar entry by one year. This is not as simple as calculating an extra year of revenue. A one-year delay increases revenue for many years because competition gradually penetrates the market. We calculated the present value of these extra earnings for both one and five years using a 10.5 percent real discount rate. We chose a 10.5 percent discount rate based on a previous study of drug research and development costs.[3] We calculated the loss for the originator as a share of its revenue.

Results

Sales Erosion for the Originator

For traditional pharmaceuticals, spending on the originator was at 42 percent of pre-competition levels at the end of the first year of generic competition and at 20 percent by the end of the fifth year. Specialty pharmaceuticals showed a similar pattern of sales decline. For biologics, spending was higher, at 91 percent of pre-competition levels at the end of the first year of biosimilar competition and at 63 percent at the end of the fifth year.

Returns for the Originator

A one-year delay in generic or biosimilar competition would increase revenue for the originator. We plot the erosion curve with and without a one-year delay. We shade the area in between the curves to illustrate the gains to the originator of a delay **(Figure 2)**.

In the first year following a delay in generic competition, traditional pharmaceuticals would earn an additional discounted 42 percent of their pre-exclusivity revenue, and over five years they would earn an additional discounted 68 percent of their pre-exclusivity revenue. For example, a drug with $1 billion in revenue would have $420 million more for the year by delaying generic competition for a year. The additional (discounted) revenue over 5 years would be $680 million. Given that some of the additional revenue would go to others in the supply chain, the drug developer would capture 58 percent of the additional revenue or about $240 million in the first year and $390 million over five years. For a specialty pharmaceutical originator, a one-year delay in generic competition would provide a similar increase in revenue.

For a biologic originator, a one-year delay in biosimilar competition would increase revenue only an additional 6 percent of their pre-loss-of-exclusivity revenue in the first year following the delay and 27 percent of their pre-loss-of-exclusivity revenue over five years.

When generic or biosimilar competition is delayed, the originator earns additional revenue because it can sell a greater quantity of products and at a higher price for payers and consumers. We use our erosion data to assess the portion of additional revenue earned by the originator from higher prices and from a greater quantity sold. We find that for traditional pharmaceuticals, 14 percent of the additional revenue earned by the originator resulting from a delay in generic competition comes from being able to sell a greater quantity of drugs, while 86 percent of the additional revenue comes from their ability to charge higher prices to payers and consumers. For biosimilars, 38 percent of the additional revenue earned comes from the loss of biosimilar sales and 62 percent of the additional revenue comes from the higher prices they are able to charge.

Supporting Analysis for 'Concern 1: Cost Burden for Patients and Payers'

Methods

We used two data sets. First, we used claims data from IQVIA for 2018 for seven top-selling drugs. We chose the seven drugs because each was in the top 25 in total spending, each had patent expiration in 2024 or later (so the results would be relevant for more years), and together they represented a variety of therapeutic areas and reimbursement types. For each drug, we obtained data on the total annual cost of the drug and the share paid by patients across three insurance types: commercial insurance, Medicare, and Medicaid. We also assessed the portion of claims for which patients paid no copayment.

Second, we used National Health Expenditure Accounts data from the Centers for Medicare & Medicaid Services (CMS). We used prescription drug spending for 2000 to 2019. The estimates include retail sales of drugs and diagnostics available by prescription. They account for rebates. CMS provided data for pharmacy drugs but not for drugs administered under the medical benefit.

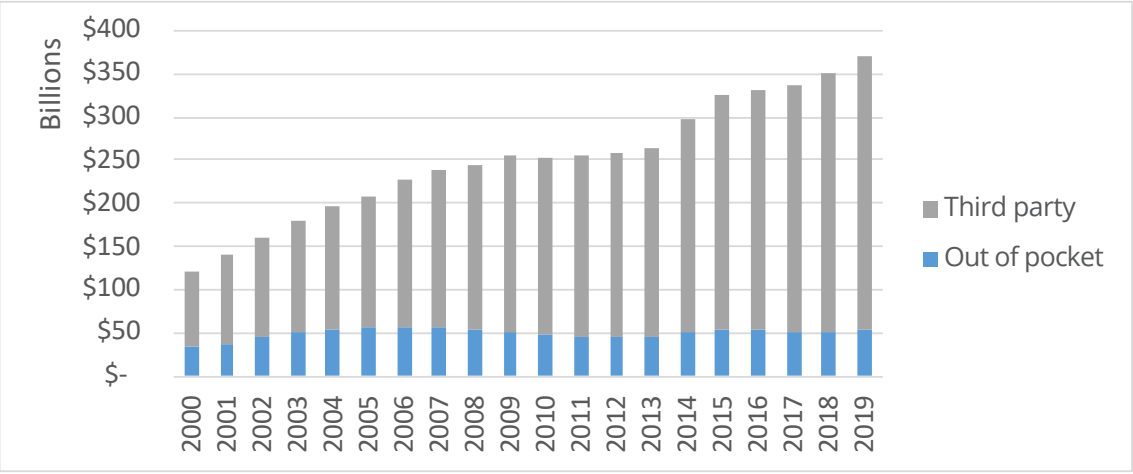
Results

For seven top-selling drugs in 2018, patients paid three percent or less of the total cost of drugs under the medical benefit, and 13% or less for drugs in the pharmacy setting. Nevertheless, these small percentages can represent thousands of dollars. For cancer drug pembrolizumab, patients paid 1.5 percent of $172,890 which is about $2600 **(Table 1)**.

For pembrolizumab and nivolumab, patients paid nothing out of pocket for 90 percent of claims. In addition, drugs dispensed under the medical benefit and reimbursed through Medicaid generally had no out-of-pocket costs. For patients with commercial insurance and Medicare, copayments were more common for pharmacy drugs. For example, the majority of commercial insurance claims for dulaglutide and rivaroxaban included out-of-pocket spending **(Table 1)**.

U.S. patients paid less than $60 billion out of pocket for pharmacy drugs each year for the past 15 years **(Figure 4)**. With over 300 million Americans, this is an average of about $200 per person per year, or less than $20 per person per month.

FIGURE 4 **Annual Retail Prescription Drug Spending**



Source: Authors' analysis of U.S. National Health Expenditure Accounts Data from the Centers for Medicare and Medicaid Services.