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Costs and Benefits of Selected Policy Tools to Promote Drug Development

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Executive Summary

The development of new drugs and biologics is critical to ensuring that the U.S. population continues to enjoy improvements in quality and length of life. However, pharmaceutical companies must balance this imperative with the need to earn economic returns when making investment decisions.¹ Some drugs, although desirable from a societal perspective, may have low expected financial returns, resulting in underinvestment from pharmaceutical companies. Such underinvestment may result from development challenges or low expected revenues. To stimulate investment in these socially productive drugs, it is necessary to understand why private pharmaceutical companies are unwilling to invest and how potential policy tools could incentivize pharmaceutical companies to invest in these drugs.

Socially productive investments have expected benefits to patients and society that exceed the expected cost of development and marketing. Several examples that have drawn recent attention for having high social value but limited expected profits to incentivize drug development include antibiotics; vaccines and therapeutics for viruses like Ebola and Zika, which primarily affect individuals in low-income countries but have outbreak risks in the United States; and medical countermeasures for chemical, biological, radiological, nuclear, and explosive threats.

Generally, pharmaceutical companies invest in developing drugs that have positive expected net present values (ENPVs), meaning that the expected returns exceed the expected costs of development and marketing. Policy interventions may address underinvestment in socially productive drugs by raising the ENPV to pharmaceutical companies through increasing risk sharing, lowering private research and development (R&D) costs, raising expected revenues, or some combination of these. Desirable policy interventions are targeted, so that they only incentivize socially productive drugs that would not otherwise be developed, and efficient, so that after including the cost of the policy intervention, the drug remains socially productive.

This report is intended to provide policymakers with a useful starting point for critically evaluating the potential effectiveness and inherent tradeoffs of policy tools aimed at spurring additional R&D efforts. The report briefly describes how seven specific policy tools could be used to encourage R&D investment for needed new drugs in the United States: (1) accelerators, (2) R&D tax credits, (3) patent and regulatory exclusivity extensions,

¹ Throughout this report, the term “pharmaceutical companies” is used to refer to any companies that develop or manufacture the desired drugs or biologics.

(4) delinkage, (5) priority review vouchers (PRVs), (6) wildcard exclusivity vouchers, and (7) advance market commitments (AMCs).²

- **Accelerators** connect innovators—often university researchers or small pharmaceutical companies—with funding for validation studies and preclinical development. Accelerators are designed to overcome what is perceived to be insufficient funding for translational R&D and early-stage product development. They reduce both the risk that a promising discovery is abandoned and the risk that an investor faces when deciding whether to support an emerging technology. Increasingly, accelerators combine funding awards with technical assistance and business development expertise.
- **R&D tax credits** subsidize R&D by allowing pharmaceutical companies to deduct a percentage of qualifying R&D costs from the company’s tax liability. R&D tax credits are intended to encourage R&D effort by lowering development costs, thereby raising the private rate of return on investment and possibly making some R&D projects that otherwise would not have been profitable into profitable projects.
- **Patent and regulatory exclusivity extensions** increase the length of time before a company faces competition from generics. During this time, a company may maintain high prices and, thus, earn additional profits to increase its return on investment.
- **Delinkage** models increase private returns by rewarding successful drug development by some means other than drug sales, sometimes with the aim of reducing drug costs for patients and payers. Prizes, especially when accompanied by terms that reduce drug prices (e.g., formal agreements that the company accepting the prize will make the drug available at a low price, or patent buyouts that allow generic pharmaceutical companies to market the drugs), are prime examples.
- **PRVs** reward successful innovation with a tradable voucher that entitles the bearer to obtain a valuable priority review from FDA. The voucher may be sold or applied to a drug candidate of the company’s choosing.
- **Wildcard exclusivity vouchers** would reward the qualifying drug with a voucher to sell or extend regulatory exclusivity on an approved drug of the pharmaceutical company’s choice for a given amount of time.
- **AMCs** aim to incentivize R&D investment by establishing a market or larger market than would otherwise exist for a needed innovation by guaranteeing a certain volume of sales or price for a given period of time (e.g., subsidizing the delivery of a new vaccine in resource-poor settings with funds raised in more affluent areas).

When considering a strategy to encourage drug development that targets a specific area of unmet need, a single policy tool or a combination of policy tools may be necessary for a comprehensive approach to achieve a drug development goal. For example, both accelerators and R&D tax credits may be needed to encourage investment in early-stage

² Note: while these seven policy tools were selected for analysis in this report, they do not represent an exhaustive list of potential policy tools for encouraging drug development. Their selection for analysis also does not necessarily indicate or imply any endorsement of these policy tools by ASPE, FDA, or HHS.

development, with the tax credit helping R&D investments attract private investors who might otherwise be drawn to shorter-term and less-risky ventures. The accelerator model further encourages early-stage investment by helping bring together scientific entrepreneurs and business experts.

To incentivize later stages of development, including costly clinical trials, incentives that aim to raise revenues for approved drug products are likely to be needed. Although combinations of these incentives could be used, the policies may be most effectively targeted by carefully considering just how much additional revenue is likely to be needed to encourage drug development for a specific need. A drug candidate with particularly high costs, a long development time, and a small potential market could likely benefit from an especially large incentive, such as that provided by wildcard exclusivity vouchers, or from a guaranteed revenue incentive, such as the revenue guarantees offered through AMCs.

While considering the most appropriate policy tool for each drug development scenario, it is also important to recognize that each approach is limited in its ability to precisely target needed drug development that would not have occurred otherwise. For example, use of a particular approach may incentivize some drug development that would have occurred without policy intervention as well as the desired drug development. Some of this mistargeting is borne broadly across stakeholder groups, but some is borne specifically by patients and payers through drug prices that exceed competitive levels and potentially delay the availability of other clinically valuable drugs. Ideal application of policy tools requires finding the balance between effective targeting and providing a large enough reward to provide a meaningful incentive for drug development.

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1. INTRODUCTION

Drug development is a difficult, time-consuming, and costly undertaking. The initial research steps leading to a drug candidate typically begin more than 10 years before a drug is approved for marketing. Many drug development projects do not progress beyond early stage research. About half reach preclinical development, 35% enter human testing, and 4% are ultimately approved by the Food and Drug Administration (FDA; DiMasi, Grabowski, & Hansen, 2016). Taking attrition and capital costs into account, the average cost to develop a new drug may be as much as \$2.6 billion (DiMasi, Grabowski, & Hansen, 2016).

From the viewpoint of society, any new drug that is expected to provide benefits that exceed the expected cost to develop and market it would be a worthwhile investment. However, from the viewpoint of a pharmaceutical company, only a drug that is expected to be profitable is typically considered to be worth the investment. When a drug investment has expected benefits that exceed expected costs, the investment is said to have positive expected net present value (ENPV). ENPV can be assessed from the societal perspective or from the pharmaceutical company, or private, perspective. The private perspective only includes the expected costs and benefits to a pharmaceutical company that is considering whether to invest in drug development. The societal perspective reflects both the public and private expected net costs and net benefits of investing in a new drug, where public costs include the cost of policies to incentivize drug development and public benefits reflect the drug's full value to patients and any other beneficiaries.

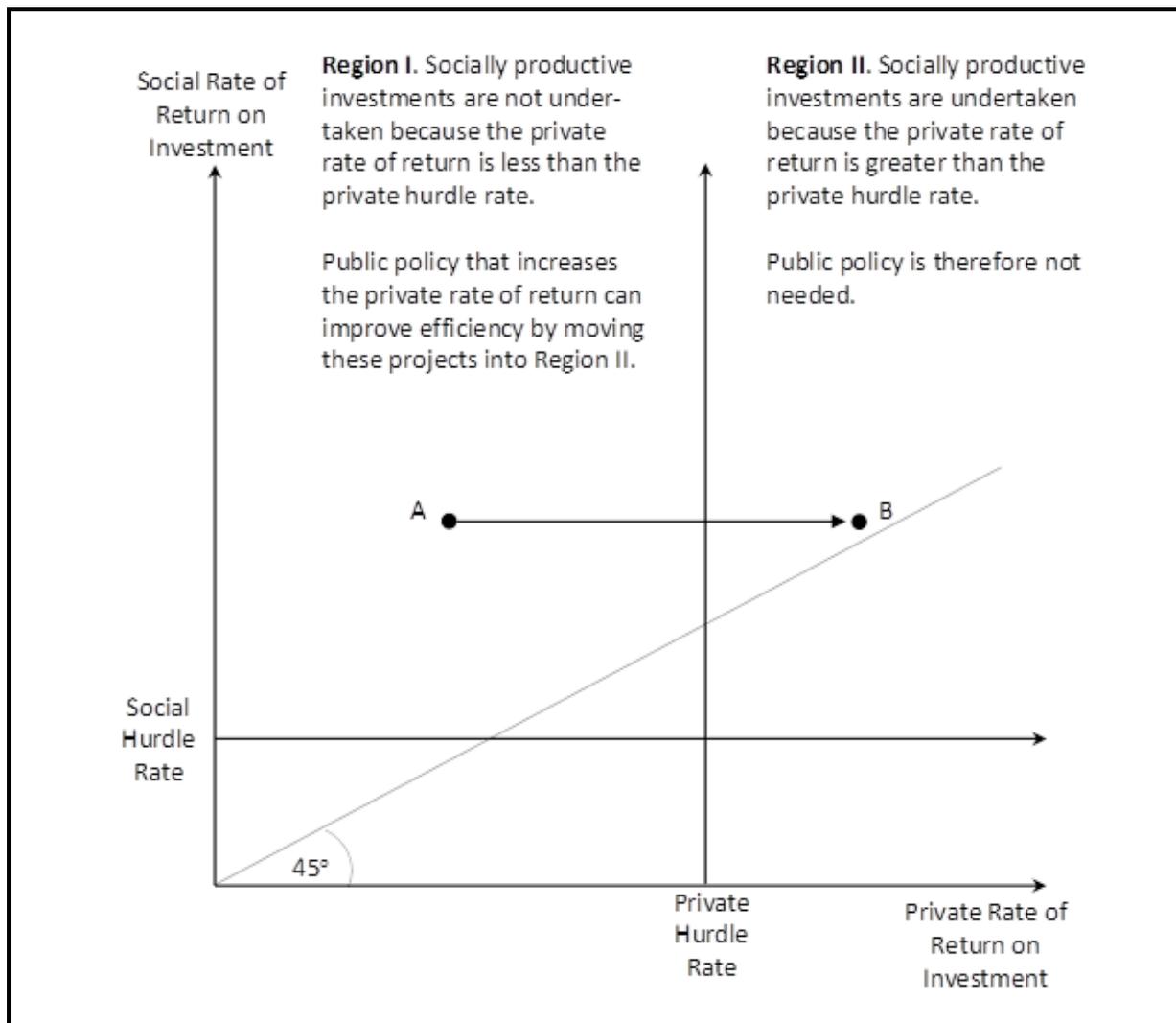
The private ENPV of a drug project may be too low to encourage pharmaceutical company investment because of high expected drug development costs, low expected drug revenues, or both. High expected costs may be driven by a long time to market or by higher than average risks of failure, such as when companies pursue a novel drug class or therapeutic approach or when they target a complex disease. Expected revenues may be low when they do not reflect the full value of a breakthrough to society (e.g., vaccines or antibiotics) or if a disease is rare and therefore has limited potential demand.

Policies to encourage R&D in drugs that address unmet medical needs might offer incentives for pharmaceutical companies to invest in drugs with positive societal ENPV. In the case of such policies, societal costs reflect pharmaceutical companies' expected R&D and marketing costs plus the government's cost of the policy.

Figure 1-1 depicts a drug with positive societal ENPV, where the social rate of return on investment exceeds the minimally acceptable rate of return (i.e., the social hurdle rate). Some investments that are desirable from a societal perspective may not have positive private ENPV. For example, point A in Figure 1-1 represents a desirable investment from a societal perspective, because the social rate of return exceeds the social hurdle rate. Yet, because the project results in a negative private ENPV (i.e., the private rate of return falls

below the private hurdle rate), it is unlikely that a pharmaceutical company would invest in the project. In this case, a successful policy would increase private returns for the project, moving it from Region I, where the private ENPV is negative, to Region II, where the private ENPV is positive.

Figure 1-1. Successful Policies Raise the Private Rate of Return or Reduce the Private Hurdle Rate



Notes: In Region I, drug development projects are socially productive. The figure is adapted from Jaffe (1998).

Policies can raise pharmaceutical companies' ENPV of drug development by addressing barriers to investments. For example, policies may focus on lowering the risks of failure, reducing or offsetting R&D costs, shortening development time, raising expected revenues (through raising the quantities sold or unit prices), or some combination of these policies. Applying such policies requires appropriate targeting and balancing of incentives, to achieve

needed development of drugs with positive societal ENPVs that would not otherwise be developed.

In this report, we analyze seven policy tools that aim to increase the expected private net benefits of R&D investment as a means to spur new drug development.³ The tools vary in their mechanisms for impacting private net benefits, as summarized in Table 1-1.

Table 1-1. Mechanisms for Each Policy Tool to Raise Expected Net Present Value of Investment

| Policy Tool | Reduces Private R&D Costs | Shortens Drug Development Cycle Time | Raises Probability of Success | Increases Revenue after Approval | Creates an Expectation of a New Market |
|---|--------------------------------------|---|--------------------------------------|---|---|
| Accelerators | • | • | • | | |
| R&D tax credits | • | | | | |
| Patents and regulatory exclusivity extensions | | | | • | |
| Delinkage | • | | | • | |
| PRVs | | | | • | |
| Wildcard exclusivity vouchers | | | | • | |
| Advance market commitments (AMCs) | | | | | • |

Sections 3 and 4 of this report analyze two policy tools that affect actual or expected development costs:

- **Accelerators** connect innovators—often university researchers or small pharmaceutical companies—with funding for validation studies and preclinical development. Accelerators are designed to overcome what is perceived to be insufficient funding for translational R&D and early-stage product development. They reduce both the risk that a promising discovery is abandoned and the risk that an investor faces when deciding whether to support an emerging technology. Increasingly, accelerators combine funding awards with technical assistance and business development expertise.
- **R&D tax credits** subsidize R&D by allowing pharmaceutical companies to deduct a percentage of qualifying R&D costs from the company’s tax liability. R&D tax credits are intended to encourage R&D effort by lowering development costs, thereby raising

³ Note: while these seven policy tools were selected for analysis in this report, they do not represent an exhaustive list of potential policy tools for encouraging drug development. Their selection for analysis also does not necessarily indicate or imply any endorsement of these policy tools by ASPE, FDA, or HHS.

the private rate of return on investment and possibly making some R&D projects that otherwise would not have been profitable into profitable projects.

Sections 5 through 9 describe five policy tools that increase the expected returns from successful drug development projects:

- **Patent and regulatory exclusivity extensions** increase the length of time before a company faces competition from generics. During this time, a company may maintain high prices and, thus, earn additional profits to increase its return on investment.
- **Delinkage** models increase private returns by rewarding successful drug development by some means other than drug sales, sometimes with the aim of reducing drug costs for patients and payers. Prizes, especially when accompanied by terms that reduce drug prices (e.g., formal agreements that the company accepting the prize will make the drug available at a low price, or patent buyouts that allow generic pharmaceutical companies to market the drugs), are prime examples.
- **PRVs** reward successful innovation with a tradable voucher that entitles the bearer to obtain a valuable priority review from FDA. The voucher may be sold or applied to a drug candidate of the company's choosing.
- **Wildcard exclusivity vouchers** would reward the qualifying drug with a voucher to sell or extend regulatory exclusivity on an approved drug of the company's choice for a given amount of time.
- **AMCs** aim to incentivize R&D investment by establishing a market or larger market than would otherwise exist for a needed innovation by guaranteeing a certain volume of sales or price for a given period of time.

Section 10 provides a deeper analysis of PRVs. Section 11 summarizes key findings, compares the policy tools, describes potential complementarities in the different policy tools that could improve outcomes, and discusses key knowledge gaps to address in future research.

2. OVERVIEW OF STUDY APPROACH

We conducted an environmental scan to obtain information from the published literature, unpublished reports and presentations, and drug policy experts about each of the seven policy tools. Our goal was to identify sources of information on the aim, usage, strengths and limitations, and other factors related to each policy tool's potential value for encouraging needed new drug development that would not have occurred otherwise. We first conducted key word searches for each policy tool in the University of North Carolina (UNC) libraries search engine and in Google Scholar. The UNC libraries search engine scans indexes of peer-reviewed articles, news stories, and government documents, searching the following: Web of Science; Scopus; PubMed, Academic Search Premier; Proquest; Google Scholar; JSTOR, CINAHL Plus; Lexis Nexis; PsychInfo; and Project Muse. Our searches included the policy tool names and alternative names or descriptions to help ensure that no relevant sources were missed. For example, we searched for "IP buyouts" to identify relevant sources for "delinkage." Because R&D tax credits are used as incentives in multiple areas, we searched for "R&D tax credits" and for "R&D tax credits" AND "drug development." These searches were initially conducted in November and December 2015 and again in January and February 2017 to update the initial findings.

We reviewed relevant sources from the database searches to develop an overview of each policy tool. We supplemented our literature review with information from additional sources identified in reference lists of articles and reports and from those provided by drug policy experts whom we interviewed in early December 2015 and January 2016. Five interviewed experts and one additional expert who worked as a project consultant provided helpful insight into the advantages and disadvantages of each policy tool and ways that tools could be better designed or targeted to achieve drug development goals.

For PRVs, we also conducted additional analyses, developing an ENPV model to explore factors that may affect the value of PRVs for incentivizing drug development and analyzing prices of sold PRVs to estimate how the value of any single PRV may decline as more PRVs are awarded to pharmaceutical companies (Chapter 10).

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3. ACCELERATORS

Accelerators seek to increase the probability that promising discoveries progress to later stages of development by funding early-stage validation, proof-of-concept, or preclinical development studies. More robust accelerator programs also provide product development, regulatory, and marketing expertise and strategize on the appropriate mix of studies that fine tune and propel a project forward. Accelerator project results may indicate that a technology should or should not move forward. They may also suggest a pivot to an alternate therapeutic area, indication, technology platform, or business model. The accelerators' goal is the availability of new products to help patients, but they recognize that for this to occur, private sector investment is necessary. Accelerator projects de-risk a technology from the perspective of a potential investor and make it more attractive for investment or acquisition (Stevens et al, 2013).

Until recently, most accelerators supported investigator-initiated projects (e.g., SPARK at Stanford University) or specific technology types (e.g., Coulter Foundation Translational Partnership Programs for medical devices). Public and non-profit funders are increasingly looking to accelerators to support promising technologies in their mission space. Examples include the National Institutes of Health (NIH) Centers for Accelerated Innovations program for heart, lung, blood, and sleep disorders and the Combatting Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) for antibiotics supported by BARDA and The Wellcome Trust.

Accelerators reduce private-sector risk, costs, and time in drug development. For a small company undertaking a drug development project, this type of funding is often critical to reducing out-of-pocket costs. For a firm that acquires a small company or a technology from a university, the accelerator may also reduce out-of-pocket costs. Although the company did not invest in the basic science and validation work that undergird the technology pre-acquisition, the more significant impact may be in the role of the accelerator project in de-risking the technology, constraining the range of potential outcomes, and lowering expected capitalized costs. The impact on total revenues is less evident, although the firm bringing the product to market may gain first-mover advantage and earlier accrual of profits.

Considering Figure 1-1, the effect of the accelerator is to reduce the required amount of private sector investment and lower uncertainties sufficiently such that the technology progresses beyond the private hurdle rate, or the minimum acceptable rate of private return. These effects are significant both for the original drug developer and for the firm that may ultimately bring the technology to market. It is also important to note that accelerators directly affect innovation. Whereas many of the other tools described in this report seek to encourage innovation by increasing potential revenues, accelerators—

particularly those targeting translational research stages at academic institutions—support the innovation process itself.

3.1 Background

Public funding for preclinical development is limited. The NIH is the largest public-sector funder, but the majority of its funding programs are focused on the development of new knowledge, not on validating findings and translational research. Venture capital has shifted away from early-stage investments to later stage ones (Fleming, 2015), widening the funding gap between basic science and product development investments. Consequently, many promising discoveries from academic settings never enter the commercialization pathway. Not only do academic innovators lack the correct type of funding, but they are often unfamiliar with product and business development steps needed to progress the technology along a commercially viable pathway (NIH, 2012). For small pharmaceutical companies, the challenge is often related more to funding than to the correct expertise.

Given the rising cost of biomedical product development, accelerators and other proof-of-concept research programs are one way to increase productivity (Paul et al., 2010). Stevens et al. (2013) suggest that programs aimed at target identification and validation can occur as early as right after discovery. As Stevens et al. (2013) point out, candidates that are successful in early proof-of-concept are inherently more valuable to pharmaceutical companies for further investment (due to decreased technical risk), which helps bridge the “valley of death” by attracting more capital investment from industry.

Accelerators supporting the earliest development stages, such as the NIH Centers for Accelerated Innovation, generally support academic researchers and clinicians. Projects are often between \$50,000 and \$400,000 for 1 to 2 years. Those targeting later preclinical stages, such as CARB-X, most commonly target small companies. Projects are often \$500,000 to \$1.5 million and 1 to 2 years in length. It is uncommon for large pharmaceutical companies to receive accelerator support, but possible in situations in which the company has an underdeveloped technology in an accelerator’s mission focus.

Accelerators competitively select proposals for funding using scientific, business, and market criteria. The selection of the programs is conducted by a team of experts within the given therapeutic area or field as well as by those with business and marketing acumen. Industry representation is common. Although the selection process varies across different accelerator models, most incorporate multiple stages of review.

Accelerators provide one or more of the following programmatic elements to successful applicants:

- funding for early-stage validation and product development studies
- scientific and technical support and program management

- regulatory expertise and strategy support
- intellectual property (IP) management and strategy support
- marketing and business planning and development support
- access to laboratory facilities and office space
- facilitated access to complementary programs and services
- skill development

These characteristics of the typical accelerator program make it particularly suited towards academic innovators and smaller pharmaceutical companies, where the incremental impact of the program is largest.

Accelerator programs may be public, quasi-public, or private. Funding from public programs are generally non-dilutive, meaning that the funding program takes no equity position in the technology. Public programs require sustained support from sponsors. Quasi-public programs may take a position in the technology or company to capture returns from successful exits to promote program sustainability.

3.2 Discussion

A policy tool is effective if it stimulates innovation that would have not occurred in the absence of the tool or if it supports innovation that otherwise would have failed. For accelerators, success hinges in large part on the selection process. The accelerator selection committee does not want to choose projects that are likely to end in failure, yet selecting only the most promising products may provide support to projects that may have progressed anyway. This feature of accelerators represents both a challenge and an unknown for the selection committee. Given that accelerators provide support in the early stages of the development process, the selection committee may not be able to discern the difference between promising projects that will likely fail without accelerator support and promising ventures that do not need accelerator support. Selection processes are designed to maximize the likelihood of selecting the most promising candidates by employing an integrated approach of science and business leaders to thoroughly vet their options (Dempwolf, Auer, & D'Ippolito, 2014).

Providing public funding for early-stage projects may raise concerns about crowding out private investment, an important issue when considering the social cost of accelerator models. However, findings suggest that public and private investment in early-stage pharmaceutical development are complementary (Toole, 2012). The structure of public accelerators supporting small companies reduces the possibility of crowding out private investment by requiring the drug developer to seek out matching private funding in addition to the public funds they receive. The possibility of crowding out private-sector investment is not a significant concern for accelerator programs targeting academic researchers.

Allocating accelerator funds to support poorly executed ideas results in a wasteful allocation of funds. The opportunity costs of losing critical research dollars reflect a social cost of accelerator programs. From a societal standpoint, though, even failed projects that receive accelerator support may be viewed as a positive outcome; because accelerators are “fast to fail,” the accelerator model may quickly free both funders and drug developers to pursue higher value projects (Dempwolf, Auer, & D’Ippolito, 2014).

Establishing an accelerator requires complex programmatic decisions about funding levels, technology focus, scope and scale of any in-house expertise, operating structure, and governance. The accelerator must be capable of cultivating a pipeline of proposed projects (particularly if limited in scope or scale). Offering services vastly increases the cost and complexity of the program, and once promised, the accelerator must be able to deliver expertise to funded innovators. Drug developers experienced in commercialization may exploit public accelerators’ nondilutive funding to delay soliciting investment and instead add value in the accelerator and thereby increase their returns later. Developers that may not have needed the accelerator support could crowd out those that do. Lastly, because they target early development stages, accelerators’ ultimate goals may not be achieved for many years following project completion. Achieving that success likely requires follow-on funding and private-sector partners.

Despite these challenges, accelerators display a flexibility in terms of targeting that other policy tools lack. For example, they can focus on particular therapeutic areas, technology types, stages of development, or types of innovator. They can be single- or multi-institution, at a regional or national scale. They can also determine what levels of risk, funding, time, and support would meet their product development objectives.

The ability to specify the desired stage of development, technology type, and therapeutic area provides accelerators with the means to target drug development. Examples of this targeting of drugs for needed therapeutic areas are already evident in existing public accelerator programs: the NIH Centers for Accelerated Innovation program targets the prevention, diagnosis, or treatment of cardiovascular, lung, blood, or sleep disorders; CARB-X only supports antibiotic technologies.

Despite successes with accelerators in the United States, the paucity of publicly available data on publicly-supported accelerators remains a gap for researchers and policymakers looking to assess the impact of accelerator programs on new drug development. Lack of data impedes objective assessment of the policy tool. However, anecdotally, accelerators are generally viewed as an important model for supporting early-stage innovation in promising technologies.

4. RESEARCH AND DEVELOPMENT TAX CREDITS

R&D tax credits subsidize R&D by allowing companies to deduct a percentage of qualifying costs from their tax liability, or, in the case of refundable tax credits, by paying the company a percentage of qualifying costs when the amount exceeds the company's tax liability. R&D tax credits aim to encourage R&D effort by lowering the cost of private R&D through shifting the burden onto the tax base, thereby making some R&D projects that otherwise would not have been profitable into profitable ones (i.e., generating positive expected net present value). Generally, targeting R&D tax credits to only incremental R&D efforts (i.e., new R&D that would not otherwise have been performed) or specific therapeutic areas is difficult for a variety of reasons, including the challenges of setting appropriate eligibility criteria and addressing information asymmetries between pharmaceutical companies and policymakers. Therefore, in addition to bearing part of the cost of new qualifying projects that would not have been undertaken in the absence of the tax credit, the tax base will also bear part of the cost of all qualifying projects that would have been undertaken even without the tax credit.⁴

Subsidized R&D costs may have an especially large impact for startups and smaller companies because those companies are more likely to need outside financing to cover R&D costs. However, nonrefundable R&D tax credits may have the least value to such companies because their tax liabilities are likely to be less than the amount of the credit. Smaller, younger firms often do not have any revenue-generating products (and thus, do not have any tax liability) and will have to carry a tax credit forward into the future, which reduces its present value. For this reason, nonrefundable credits are unlikely to attract new innovators (Rao, 2011). Refundable tax credits, which are essentially as good as cash, are valuable to both large and small firms. Transferable tax credits that can be sold on the open market have also been considered, but they would likely disproportionately benefit larger companies, because smaller firms are more likely to transfer their tax credits, incurring substantial transaction costs. The R&D tax credits that we highlight in Section 4.1 are non-transferable and non-refundable.

4.1 Background

Several R&D tax credits relevant for biomedical innovation are currently in place in the United States, and others have been proposed. Several key examples are summarized in Table 4-1.

⁴ A tax credit amounts to risk sharing with the government because a company can terminate its operations if its drug candidates or lead molecules fail on a later stage in the R&D process (Baraldi et al., 2016). Tax credit policy not only pays for success but also shares in the cost of R&D that may or may not produce a successful innovation.

Table 4-1. R&D Tax Credits in the United States for Biopharmaceutical Innovation

| Example | Description | Type |
|--|---|-----------------------------------|
| Drug Development Tax Credits | | |
| Orphan Drug Tax Credit (ODTC) | Among other things, the U.S. Orphan Drug Act (ODA) established an income tax credit equal to 50% of human clinical trial expenses for eligible drugs that treat rare diseases with a prevalence rate below 200,000 Americans. | Nonrefundable, total volume-based |
| Qualifying Therapeutic Discovery Project Tax Credit | This tax credit for small companies with less than 250 employees supports work that helps meet an unmet medical need, brings down long-term U.S. health care costs, or advances a cure for cancer. This income tax credit of 50% can be applied at all stages of R&D. | Refundable, total volume-based |
| General Tax Credits | | |
| Research and Experimentation Tax Credit (commonly referred to as "R&D Tax Credit") | The federal R&D Tax Credit is a general business tax credit for companies that incur R&D costs in the United States. It was originally introduced in the Economic Recovery Tax Act of 1981 and is an incremental tax credit to boost R&D in the experimental/laboratory stage. The federal credit allows corporations to take a credit against their tax liability equal to 20% (or 14%, depending how the base amount is calculated) of their current year's qualified R&D expenditures in excess of a base amount on their federal corporate R&D tax return. | Nonrefundable, incremental |

Notes: *Total-volume based* refers to R&D tax credits that can be applied to qualifying gross R&D expenditures. *Incremental* refers to R&D tax credits that can be applied only to extra R&D, above a company-specific reference level.

In addition to the programs described in Table 4-1, 45 states currently offer their own R&D tax credit programs similar to the federal tax credit (Deloitte, 2015). A number of states also offer targeted incentives on R&D spending in specific fields or particular zones (e.g., enterprise zones) or for other specific attributes (e.g., small companies, startups) (Wilson, 2005).

In an analysis prepared for the Biotechnology Industry Organization and the National Organization for Rare Disorders, Ernst & Young (2015) estimated that the ODTC combined with the general R&D tax credit offers an average present value savings of \$138.8 million in development costs for established drug developers. The ODTC alone on average leads to an estimated \$122.1 million in present value annual savings (Ernst & Young, 2015). For younger companies that are at the pre-revenue stage, the ODTC and the R&D tax credit have limited value because they are nonrefundable and nontransferable.

The impact of R&D tax credits may be highly sensitive to their design and organization, but empirical studies on the effects of design and organizational features are scarce. One aspect

that is relatively well studied is whether incremental schemes—when R&D tax credits are applied only to extra R&D above a company-specific reference level—perform better than volume-based schemes—when R&D tax credits are applied to qualifying gross R&D expenditures. Both types of designs have been found to result in additional R&D expenditure, but the evidence on which type of scheme is more effective is mixed (CPB Netherlands Bureau for Economic Policy Analysis, 2014).

4.2 Discussion

An advantage of tax credits is that they are relatively straightforward to implement and entail lower administrative costs than other, more complex policy tools (Renwick et al., 2016). However, the direct cost of the tax credit program can often be large and difficult to project (Rao, 2011). Rao (2011) proposes a cap to address this problem, but notes that a cap may dilute the effect of the program.⁵ The Qualifying Therapeutic Drug Discovery Tax Credit is the only program with a cap. The direct cost of the ODTC was nearly \$2 billion until 2008 and, at the time, was projected to cost an additional \$1.9 billion between 2008 and 2012 (Yin, 2008). More recently, forecasts of estimated tax expenditures from 2011 to 2020 show a total estimated cost of \$14.5 billion for the ODTC with annual costs forecasted to increase over time. The R&D tax credit, which is used in a variety of industries, has a total cost over the same period of \$35.8 billion (Joint Committee on Taxation, 2012; Joint Committee on Taxation, 2017).

An implementation challenge for R&D tax credits involves the degree to which the tax credit can be effectively targeted to specific research areas (e.g., stages, therapeutic areas) without increasing compliance costs dramatically. For example, incremental schemes result in higher administrative and compliance costs than schemes that apply to a company's gross R&D spending⁶ (CPB Netherlands Bureau for Economic Policy Analysis, 2014). The compliance costs of the ODTC and R&D tax credit have not been published. Administrative practices, such as offering an online application or one-stop shop for tax credit applications, may reduce both government and private compliance costs.

Not only are compliance costs an issue with more targeted tax credit programs, but criteria for eligibility of R&D costs need to be carefully elaborated. For instance, in their consideration of policy tools that could be used to spur antibiotic development, driving reinvestment in research and development and responsible antibiotic use (DRIVE-AB) pointed out the challenge of determining how to elect the R&D costs for an immunology-based project whose output results in both antibiotics and nonantibiotic drugs (Baraldi et

⁵ Because of the high volume of applications for the Qualifying Therapeutic Discovery Project Tax Credit, value of awards diluted to about \$244,749 on average, resulting in less than 50% project cost recovery for most applicants (Rao, 2011).

⁶ Direct costs refer to the foregone tax revenues associated with tax credits. Compliance costs refer to administrative costs associated with tax credits that are borne both by government and the private sector.

al., 2016). The tax code may not be the optimal place to make such distinctions because it gives implementing agencies limited leeway to tweak and refine criteria in accordance with shifting public health priorities.

Another key implementation decision for a tax credit is whether it is total-volume based or incremental. Incremental tax credits attempt to lessen the problem of rewarding companies for R&D that they would have pursued anyway, but implementing an incremental tax credit has a variety of practical challenges. For example, the reference level of spending for the R&D tax credit in the United States is controversial because companies must increase R&D each year to claim the credit and validate past years' expenditure. Incremental schemes can also distort company behavior because they can cause companies to cycle R&D to maximize tax benefits (European Commission, 2008). Furthermore, administrative and compliance burden is a barrier to uptake, particularly for small firms, and lack of clarity about key statutory definitions (i.e., qualifying expenses) raises transaction costs for all firms wishing to take advantage of the credit (Rao, 2011).

It is also important to consider the degree to which a tax credit subsidizes R&D that would have been undertaken otherwise, which can result in a loss of tax revenue with no tangible benefit (Rao, 2011). Existing literature finds that supply-side tax credit policy encourages increased R&D activity as one would expect, but there are concerns that the observed increase may be biased. For example, Yin (2008) found that the ODA (including both the tax credit and other key provisions) led to a sustained 69% long-term increase in the annual flow of new clinical trials for established rare diseases that policymakers sought to influence. The effect of the ODA on rare diseases with the smallest markets was temporary, limited to the immediate years after ODA's passage. While the observed increase for established rare diseases was sizeable, Yin points out two potential limitations regarding what would have otherwise happened that may bias the results upward: (1) anticipation of the ODA may have led firms to delay clinical trials prior to the ODA and (2) drugs that would have been developed anyway may have received subsidization due to approvals sought for rare subsets of more-prevalent diseases. In a follow-up paper, Yin (2009) estimated that half of the total R&D response to the ODA is in these subsets of rare diseases that are more prevalent than rare diseases with much smaller patient populations.

Another challenge for implementation is the degree to which a tax credit encourages R&D with the largest possible spillover benefits. Studies of the European R&D tax credits show that each €1 of foregone tax revenue on R&D tax credits raises expenditure on R&D by less than €1 (European Commission, 2008; Mulkey & Mairesse, 2013). However, this measure of cost-effectiveness does not necessarily mean that R&D tax credits are inefficient from a net social welfare perspective. The key parameter is the degree of spillover benefits from R&D and whether those exceed compliance costs and opportunity costs of public funding. A study of the Canadian Scientific Research and Experimental Development found a positive net welfare gain on the order of 11% (Parsons & Phillips, 2007). Simulations conducted by the

European Commission in 2008 using Dutch data also indicated a positive net welfare gain that is robust to sensitivity analysis (European Commission, 2008).

Overall, the primary disadvantage of R&D tax incentives is that unless stipulated otherwise, firms tend to first invest in projects with the highest private, rather than social, returns (Hall and Van Reenen, 2000). For example, high-risk, early-stage research tends to attract less private sector investment and, thus, has a real need for policy intervention. However, R&D tax credits tend to be more effective at inducing later-stage development with greater private returns in present value terms, which is characterized by sufficient levels of private investment.

To maximize the efficacy of tax credits for stimulating R&D that would not have occurred otherwise, policymakers could in theory set eligibility criteria to target R&D expenses only in early-stage development, perhaps at the preclinical stage. Also, if a goal of policy is to draw new innovators into an area or to incentivize younger, smaller firms, policymakers could consider making tax credits refundable and setting eligibility criteria based on company size (such as the Qualifying Therapeutic Drug Discovery Tax Credit) or company age. Additionally, given that tax credits are limited in their ability to encourage new R&D for diseases with limited revenue potential, the interaction of tax credits with other pull mechanisms could be further explored where there are market failures.

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5. PATENT AND REGULATORY EXCLUSIVITY EXTENSIONS

Patents and regulatory exclusivities shield drugs and biologics that qualify for these protections from competition from generic drugs or biosimilars for a set period of time to help encourage R&D investment. Even with these protections, some R&D investments that could yield socially beneficial drugs may not be undertaken because of low expected private returns to investment. Patent and regulatory exclusivity extensions aim to address the lack of investment in needed drug development by extending the length of protection from generic competition, thus raising ENPV. To be successful, patent and regulatory exclusivity extensions need to raise the ENPV enough to encourage drug development (Figure 1-1).

Patents are granted by the United States Patent and Trademark Office anywhere along the development timeline for a drug (FDA, 2014). Patents grant exclusive rights to an invention for 20 years from the date of filing (FDA, 2014). Under the Hatch-Waxman Act, pharmaceutical products may have their patent life extended by up to 14 years to make up for patent time lost to conducting clinical trials and obtaining FDA review. Patent holders are responsible for monitoring any possible infringements and pursuing legal action as needed to protect their rights.

Additional protection is provided by regulatory exclusivities, which are administered by FDA under the Federal Food, Drug, and Cosmetic Act and granted at the time of FDA approval (Thomas, 2013). Regulatory exclusivities provide protection from competition for a specified period after FDA approval and may run concurrently with time on patent or not. Regulatory exclusivities may be divided into two categories: marketing exclusivity and data exclusivity. Marketing exclusivity prohibits competitors from obtaining FDA approval for a generic version of the drug during the exclusivity period (Thomas, 2013). Data exclusivity does not prohibit competitors from seeking FDA approval but instead prohibits generic competitors from using a protected drug's data in their application. As Thomas (2013) points out, although data exclusivity does not prevent a generic competitor from conducting its own clinical trials and submitting a drug application, the high cost of conducting clinical trials and the relatively low expected return on investment for generic products means that data exclusivity effectively excludes competition.

After patents and regulatory exclusivities expire, up to 80% of a drug's market may be captured by generics (The Lancet Oncology Editors, 2015). Extensions of patents and regulatory exclusivities, which further delay generic entry, may raise expected revenues, potentially encouraging development for targeted drugs that otherwise would not have occurred. Yet, the reason many unmet medical needs go unaddressed is because of a small market, such as in the case of rare diseases. If expected revenues for a targeted drug are low relative to R&D costs, then extending patent life or exclusivity periods is unlikely to raise expected revenues enough to encourage drug development. Orphan and other drugs

that address relatively uncommon conditions may have lower private R&D costs because of the relatively small clinical trials required for a drug application (ASPE, 2016). They may also be priced much higher than nonorphan drugs, so that a policy to extend patent life or exclusivity periods for these drugs may raise expected private revenue enough to encourage development. The mean cost of new drug development for orphan drugs has been estimated to be about \$1 billion, in contrast to up to \$2.6 billion for nonorphan drugs (ASPE, 2016). In terms of pricing, EvaluatePharma (2017) reported that 2016 orphan drugs averaged \$140,000 per patient compared with annual prices of \$28,000 per patient for nonorphan drugs.

5.1 Background

Key U.S. laws establishing patent life and periods of regulatory exclusivity and the outcomes incentivized by each are summarized in Table 5-1. As shown in the table, regulatory exclusivity periods are not standardized across all U.S. drug products. For example, a qualifying drug containing a new chemical entity (NCE), which is a drug with a new active component that has not been previously approved by FDA (FDA FAQs, 2017), receives a 5-year data exclusivity. A qualifying new orphan drug receives a 7-year marketing exclusivity, and a qualifying biologic receives a 12-year marketing exclusivity. The effective periods of protection from competition are often longer than those shown in the table because, under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), review of a generic drug application may be put on hold for 30 months to allow for court review of potential patent infringements (Rumore, 2009).

Regulatory exclusivities may provide back-to-back periods of protection from generic competition. For example, if a drug containing an NCE also receives approval as a qualified infectious disease product under the GAIN Act, 5 years of data exclusivity is added, for a combined 10 years of regulatory exclusivity. If the same drug further qualifies for the pediatric exclusivity extension, it will have its regulatory exclusivity period lengthened to 10.5 years.

Some studies have analyzed the extent to which longer patent or exclusivity periods or extensions, such as those specified in ODA and GAIN, incentivize the development of targeted drug products. Grabowski, DiMasi, and Long (2015) examined whether ODA, which included tax credits and government grants in addition to a 7-year marketing exclusivity period for qualifying orphan drugs, incentivized drug development that would not have occurred otherwise. Between 1984 and 2011, FDA granted 2,626 orphan designations for drugs in development and approved more than 350 orphan drugs (Grabowski, DiMasi, and Long, 2015), while fewer than 10 products for rare diseases were approved and marketed in the 10 years before the passage of the ODA (Long and Works, 2013). These results indicate that more orphan drugs were approved following passage of ODA, but some of those drugs

may have sought approval even in the absence of the 7-year marketing exclusivity and other incentives.

Table 5-1. U.S. Laws that Grant Patent or Regulatory Exclusivity and Key Features

| Legislation | Incentivized Outcome | Length and Features of Regulatory Exclusivity or Extension | Main Criteria to Qualify |
|--|---|---|---|
| Hatch-Waxman Act | Drug containing an NCE | 5-year data exclusivity | Qualifying products must include new active ingredient (Thomas, 2013) |
| Hatch-Waxman Act | New formulation of previously approved drug | 3-year data exclusivity | Conduct new clinical studies typically involving different dosages, new indications, or a switch from prescription to over-the-counter designation (Thomas, 2013) |
| Hatch-Waxman Act | New drugs or new formulations | Extends time on patent up to 14 years to compensate for patent time lost during clinical trial and FDA approval phases | Drug with an active patent prior to clinical testing or FDA approval (Sokal and Gerstenblith, 2010) |
| Hatch-Waxman Act | Generic drug competition | 180 days of marketing exclusivity | First generic drug to submit for FDA approval (FDA, 2015a) |
| Biologics Price Competition and Innovation Act of 2009, included in the Patient Protection and Affordable Care Act | Biologics | 12-year regulatory exclusivity, during which a biosimilar may not be approved; 4-year marketing exclusivity, during which biosimilar application may not be submitted | Qualifying biologics obtain a 12-year regulatory exclusivity period (FDA, 2015b) |
| Orphan Drug Act | Drug products that treat a rare condition affecting less than 200,000 people in the United States | 7-year marketing exclusivity | Treat a rare condition or condition that affects fewer than 200,000 people, without reasonable expectation that drug sales would exceed development costs (Thomas, 2013) |
| FDA Modernization Act of 1997 and Best Pharmaceuticals for Children Act of 2002 | Pediatric testing of approved drug products | 6-month data exclusivity extension, known as pediatric exclusivity | FDA requests studies in pediatric populations and specifies requirements to obtain extension for approved drug (Thomas, 2013) |
| Generating Antibiotic Incentives Now (GAIN) Act, part of the FDA Safety and Innovation Act of 2012 | Qualified infectious disease product (QIDP; i.e., antibacterial or antifungal drug) | 5-year data exclusivity extension | For drugs that treat drug-resistant tuberculosis, gram negative bacteria, or <i>Staphylococcus aureus</i> , extension added to data exclusivity award (e.g., for qualifying orphan drug or NCE) |

Because the GAIN Act was passed 5 years ago, it is too soon to fully assess whether its exclusivity extension provisions have had an impact on antibiotic innovation. However, a recent U.S. Government Accountability Office (GAO) report describes that as of December 31, 2015, 101 antibiotics had been designated as QIDPs under the GAIN Act (GAO, 2017). Six of these drugs had been approved as of October 2016; five were determined to be eligible for a 5-year marketing exclusivity extension (GAO, 2017). Because all of the approved drugs were in the later stages of development when the GAIN Act was passed, development of these drugs cannot be attributed to the exclusivity extension. Yet, the large number of drugs with QIDP designation since 2012 suggests that the GAIN Act provisions may be working to incentivize investment in QIDPs.

The pediatric exclusivity extension may be especially attractive to pharmaceutical companies because the award is granted regardless of findings from pediatric clinical studies, making it low risk to pursue (Li et al., 2007). FDA determines whether information from clinical studies in children could be of value and, if so, invites a company to complete pediatric studies to qualify for the pediatric extension. The pediatric exclusivity provisions have resulted in many pediatric drug and labeling changes. Vernon et al. (2012) reported that 386 drug products had a pediatric labeling change between October 1998 and June 2010 resulting from the pediatric exclusivity provision. Labeling changes have included expanded age information, new or enhanced safety information, dosing changes, and pharmacokinetic differences—all important information for guiding prescription drug usage in a pediatric population.

5.2 Discussion

Patents and exclusivity protections for drug products have played an important role in encouraging drug development in the United States (Cohen et al., 2000; Cockburn, 2004; Grabowski, DiMasi, and Long, 2015). Building on the success of these protections, lawmakers have used patent or exclusivity extensions to incentivize new drug development for products that target unmet medical needs. Extensions may be a popular option for lawmakers because no direct financial outlays are required to implement them.

Despite this advantage, extensions also have several disadvantages. First, extensions will only raise expected revenues if robust demand exists for the targeted drug or if the price is high enough that extensions may make ENPV positive. Yet, the market for many unmet medical needs is likely too small to generate the level of demand necessary to spur new drug development. Second, because extensions are added at the end of existing patent or exclusivity protections, which may be 10 or more years after beginning clinical trials, the high opportunity cost of time means that the expected value of extensions at the time of early-stage R&D investment may be too low to spur investment except for drugs with large expected revenues (Outterson et al., 2015). In later stages of development, however, when the probability of FDA approval is higher and the length of time until patents or exclusivities

expire is shorter, the value of an extension is much greater (Renwick, Brogan, and Mossialos, 2015). Third, the value of a patent or exclusivity extension is highly uncertain at the time of early-stage investment decisions. Extensions cannot prevent competition from nonidentical drugs that treat the same condition, and such drugs would reduce the size of the potential market for a new drug. Pharmaceutical companies also face uncertainty in the availability of an extension policy when a drug candidate receives approval for marketing; policies may change or be eliminated by the time FDA approval is obtained. Finally, for products with sufficient demand, expected returns from extensions may be larger than the expected returns needed to spur investment (Li et al., 2007; Baker-Smith et al., 2008; Nelson et al., 2011).

If extension policies lead to increases in the development of needed new drugs, those drugs may produce social benefits in terms of increased quality and length of life for patients who gain access to needed new drugs (Lichtenberg, 2013; Vernon et al., 2012). However, by delaying competition from generic drugs, extensions result in considerably higher drug prices than would otherwise be charged. These added costs are borne by U.S. consumers, the U.S. government, and other third-party payers. Payers may choose not to cover the costs of drugs if they perceive that treatment costs exceed the value of new treatments to patients. And patients may forego taking high-cost drugs, thereby delaying improvements in population health until a generic alternative is available.

A key design challenge is to effectively provide an incentive for needed drug development while not overly restricting generic competition. Current U.S. policies may not be targeted enough to ensure that the extension applies only to the targeted outcomes. In addition, profits from existing extension policies may far exceed the levels needed to incentivize the desired drug development. Because the reward from exclusivity extensions is determined in the market, the highest revenue drugs stand to benefit the most (Renwick, Brogan, and Mossialos, 2015). In examining the pediatric exclusivity extension, Olson and Yin (2015) found that innovators chose to conduct pediatric studies for high-revenue drugs over drugs that would have been medically important to children and for older drugs with less remaining patent life over newer drugs.

One policy design alternative that could improve targeting of extensions is to offer extensions only for drug categories that require longer, riskier, and more expensive, stage III clinical studies (Kesselheim et al., 2017). The rationale for this approach is that R&D costs for such drugs are so high that an extended period of protection from competition may be needed to spur investment in R&D. However, such an approach will only be successful if drug product demand and anticipated prices are sufficient to spur investment. Another approach to better target regulatory extensions is to limit the terms of the extension based on drug revenues. The extension rewarded for a given drug or biologic might be set to expire after crossing a given threshold of sales, such as \$2 billion.

Extensions are effective only for products with robust expected demand. Pharmaceutical companies need a reliable market for their product over the extension period for the increased revenues to spur innovation. Such robust demand may come from having a relatively constant number of patients in need of a novel treatment or a consistent number of patients that suffer from a severe acute illness each year.

Large pharmaceutical companies that can afford to invest in costly clinical trials and bring a product to market clearly stand to benefit from extensions, because they are more likely to remain in business for long enough to benefit from an extension. However, smaller pharmaceutical companies that develop a drug that qualifies for an extension may also benefit, even if they plan to sell the drug prior to seeking FDA approval to market the drug. The reason smaller companies may benefit is because extensions raise the ENPV for a qualifying drug, so start-ups or other smaller drug developers could command a higher price for selling a drug in development that is expected to receive a regulatory extension upon approval.

6. DELINKAGE

A delinkage mechanism is any means of rewarding successful drug development, or an intermediate step toward drug development, other than through sales of the resulting drug. The mechanism specifies the nature and amount of the reward, sets forth criteria for award, and provides a framework for determining when criteria have been met and for making awards. Delinkage mechanisms thus provide a return on R&D investment that is at least partly independent of volume-based sales revenues for the resulting product. The goal of delinkage is to incentivize the appropriate amount of R&D investment over time to obtain needed new drugs (i.e., achieving dynamic efficiency) without negatively altering the mixture of drugs available to patients (i.e., achieving allocative efficiency).

Perhaps the most straightforward examples of delinkage mechanisms are innovation inducement prizes. Prizes that are also linked to patent buyouts or agreements to provide a drug at cost completely delink return on investment from sales revenues; prizes not linked to such conditions achieve partial delinkage. Partial delinkage mechanisms provide an additional, nonmarket-based reward for successful innovation, which increases the expected return on R&D. Complete delinkage mechanisms can be designed to achieve other aims, such as affordable access to treatments, conservation of antibiotics, or promotion of knowledge sharing.

Prizes that reward intermediate stages of innovation can reduce the expected cost of drug development. For example, a prize can reward meaningful progress towards a new drug, despite there being several years and multiple risky development steps before having an approved drug. Such prizes could reduce the expected capital cost because pharmaceutical companies would then have some chance of an earlier payoff, allowing them to avoid carrying development costs all the way through to drug approval. Similarly, such models could also reduce investment risk, which could lower the rate of return demanded by investors, further decreasing capital costs.

Prizes can also indirectly lower the cost of developing new drugs by stimulating complementary innovations in knowledge and tools that are useful in the drug development process. One such prize competition, the Prize4Life ALS Biomarker Prize, launched in 2006 and awarded in 2011, may eventually be credited with greatly reducing the cost of Phase 2 clinical trials for ALS drugs. A more detailed discussion of this example is provided later in this chapter.

6.1 Background

The rationale for and expected effects of delinkage are perhaps best described through examples. Delinkage models have been proposed to stimulate antibiotic R&D, which provides a lower return on investment than other drug categories for several reasons.

Antibiotic prices are kept low by pharmacies' common practice of using generic antibiotics as a loss leader (pricing them at or below cost to draw customers) and hospitals' inclusion of antibiotics in bundled payments (giving them strong disincentive to introduce more expensive new antibiotics unless necessary). Revenues are further limited by declining per-capita prescriptions, reflecting changes in best practice toward conservation and stewardship. Government funding for antibiotic R&D has been flat (Outterson, et al., 2015). The most serious efforts to implement complete delinkage models (exemplified by DRIVE-AB, discussed below) are happening in antibiotics.

Delinkage models are especially attractive for stimulating antibiotic R&D because of the need to overcome two problems at once. Policies are needed to increase the incentive to develop antibiotics while at the same time encouraging stewardship (i.e., conservation or sustainable use) of new antibiotics, two goals that are conflicting under traditional models that reward successful R&D with volume-based sales revenues (So et al., 2011).

Delinkage models have also been championed as a means of maintaining incentives for innovation while improving patient access to drugs by keeping prices low and encouraging greater openness with respect to intellectual property, knowledge sharing, and collaboration to accelerate discovery (UNITAID, 2016).

Proposed legislation has also described involuntary delinkage models, like the Medical Innovations Prize Fund Act of 2011 and the Prize Fund for HIV/AIDS Act, which would have eliminated legal monopolies on pharmaceutical sales. Delinkage might also describe many forms of innovation inducement prizes, where the amount of the prize itself is not based on a product's sales revenues but rather on certain prespecified criteria being met (by a product, a prototype, or simply an idea). When a prize (i.e., any form of reward, including, for instance, a voucher for priority review or exclusivity extension) can be accepted by a company without, in exchange, foregoing any part of its exclusive rights to market the product for which the prize is awarded, then the prize may make the total rewards for developing the product less sensitive to the size of the market, and in that sense, achieves partial delinkage.

There is renewed interest in prizes as a mechanism to incentivize meaningful progress towards drug development in the public interest. On January 4, 2011, President Obama signed into law the America COMPETES Reauthorization Act, granting all Federal agencies broad authority to conduct prize competitions to stimulate innovation.⁷ Section 2002 of the 21st Century Cures Act, enacted in December 2016, includes provisions for NIH to support prize competitions with certain goals, building on the authorities under the Stevenson-

⁷ Section 105 of the Reauthorization Act (Public Law 111-358) expanded Federal agencies' authority to offer prizes by amending the Stevenson-Wydler Technology Innovation Act of 1980, adding Section 24 (Prize Competitions), <https://www.gpo.gov/fdsys/pkg/PLAW-111publ358/pdf/PLAW-111publ358.pdf>.

Wydler Technology Innovation Act, as amended by Section 105 of the America COMPETES Reauthorization Act.

These and other examples of prizes and delinkage models are described below. A final section offers a discussion of policy issues, understanding that prizes and delinkage models to spur drug development are new and few, and it is too soon to draw conclusions about their effectiveness in different situations.

6.1.1 DRIVE-AB

DRIVE-AB, a project of the European Union’s Innovative Medicines Initiative, New Drugs for Bad Bugs, has proposed and is pursuing implementation of two delinkage models, among a short list of incentives to stimulate different types of antibiotic R&D (DRIVE-AB, 2016). Insurance licenses, which are described as at least a useful intermediate step toward delinkage, would be annual licenses “paid to a manufacturer to have access to a specific antibiotic, up to a specified volume” (DRIVE-AB, 2016, 16). Prior to the development of a new antibiotic, expressions of interest (typically by hospitals interested in securing access to rarely used antibiotics) in such licensing arrangements offer pharmaceutical companies an expected return on their R&D investment. Market Entry Rewards are commitments—issued by a government, global body, or coalition of partners—to “pay a predefined amount to an innovator that achieves regulatory approval for a new antibiotic meeting specified requirements, including target pathogens” (DRIVE-AB, 2016, 19). The model is based on a proposal by Rex and Outterson (2016) and includes a base payment for meeting minimum criteria and bonuses for meeting additional criteria. In the most complete delinkage model, pharmaceutical companies accepting payment would be bound by conditions that would eliminate volume-based sales revenues, including pricing at cost and foregoing all promotion and marketing except for “assisting national experts in correctly placing the new antibiotic into national guidelines” (DRIVE-AB, 2016, 19). In a hybrid, partial-delinkage variant, smaller market entry rewards would be paid and less stringent conditions placed on companies’ pricing, still retaining some requirements for activities to promote conservation or sustainable use.

6.1.2 ALS Biomarker Prize

The \$1 million ALS Biomarker Prize was launched in 2006 to help overcome a barrier to developing new ALS treatments: Without a tool to effectively measure the progression of ALS in patients, taking a drug candidate into clinical trials was an expensive and risky proposition. Trials based on clinical endpoints like paralysis and death required large numbers of patients and could be prohibitively costly without a sufficiently reliable signal that the drug had a reasonable chance of being proven effective. In 2011, the prize was awarded to Dr. Seward Rutkove for his development of electrical impedance myography, a technology with the potential to accurately measure the progression of ALS—and therefore a drug’s effect on that progression—in short-term studies (Prize4Life, 2017).

Incorporating such a tool into clinical trials is a lengthy process, and it is too soon—even 6 years after the prize was awarded—to assess the ultimate impact of Dr. Seward’s innovation and the prize competition on ALS drug development. In a review of 20 years of ALS clinical trials citing masitinib and edaravone as promising candidates nearing approval, Petrov et al. (2017) did not mention electrical impedance myography. This does not mean that the prize competition did not lead to successful new drugs, but it does suggest that novel ideas, which can in fact be sparked by prizes that are small relative to the overall cost of drug development, may take a long time to have measurable effects on the drug development process.

The full impact of the prize also includes its effect on stimulating creative thought about the problem of an ALS biomarker. In addition to the final award to Dr. Rutkove, Prize4Life awarded 5 intermediate “thought” prizes in 2007 and two “progress” prizes in 2009. Over 1000 solvers in more than 20 countries participated, roughly two-thirds from outside traditional ALS research fields, and the \$1 million prize mobilized more than \$4 million in investment by participants (Prize4Life, 2017).

6.1.3 U.S. Federal Agency Authority for Prize Competitions

Among the prize competitions launched by U.S. federal agencies after the passage of the America COMPETES Reauthorization Act, the Antimicrobial Resistance Diagnostic Challenge, cosponsored by NIH and the U.S. Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response, aims to stimulate innovative ideas for rapid point-of-care laboratory diagnostic tests to identify drug-resistant bacteria. Like the ALS Biomarker Prize, this prize competition is staged and has the potential for multiple awards. Ten semifinalists from a field of 74 submissions were announced in March 2017. Each received \$50,000 to develop their concepts into prototypes for the second phase of the challenge, which is open to all. In the second phase, 10 finalists will be selected to develop their prototypes for a final phase, in which up to three winners will be selected (NIH, 2017).

More prize competitions like the Antimicrobial Resistance Diagnostic Challenge administered by federal agencies may appear in the future, as presaged by the inclusion of prize provisions in recently passed legislation. Section 2002 of the 21st Century Cures Act, passed in December 2016, directs the NIH to support prize competitions. Although Section 2002 makes no explicit mention of Alzheimer’s disease, its title is “EUREKA Prize Competitions,” and it is based on the earlier proposed Ensuring Useful Research Expenditures Is Key for Alzheimer’s (EUREKA) Act.

The Senate version of the proposed EUREKA Act had identified several types of breakthroughs to be rewarded with prizes. The prize criteria suggest that the intent was to reward innovations that would otherwise be unlikely to generate a large return on investment. For example, one prize would have been for identification of scalable, noninvasive means of early detection and diagnosis of Alzheimer’s disease. The proposed

EUREKA Act is notable, as it sought to stimulate desired innovations that pharmaceutical companies likely would not have undertaken on their own. Whereas a disease-modifying treatment for Alzheimer’s disease would be enormously valuable to the pharmaceutical company developing and marketing it, developing new knowledge and tools that could accelerate that process are privately less rewarding. The proposed legislation was therefore a creditable effort to target incentives where they are most needed.

6.2 Discussion

Where delinkage models are advocated, it is usually with a dual intent—to stimulate R&D by providing added incentive while also moving away from the traditional business model where the return on R&D investment is generated by marketing a drug under patent. This second intent may be motivated by the aim to ensure sustainable use of antibiotics, promote affordable access for patients, or encourage open and collaborative innovation. Although DRIVE-AB is on the road to implementing two delinkage models—insurance licenses and market entry rewards—together with other interventions to promote antibiotic innovation and sustainable use, currently no working delinkage mechanisms (i.e., no complete delinkage mechanisms) provide the opportunity to observe and measure impacts.

However, some prize competitions (i.e., innovation inducement prizes) can be observed. Although such prizes are by no means new, their application to stimulate medical product innovation is relatively new, and examples are few. One such example, the ALS Biomarker Prize, looks in every way like a success: a barrier to innovation was identified, a technology to overcome the barrier was described, a prize competition was launched in 2006, and the prize was awarded to a winning technology in 2011. A conservative estimate of the impact of the prize competition on ALS research would likely find that it greatly eclipsed the cost of the prize competition (the \$1 million grand prize together with the roughly \$4 million in outside investment mobilized by the prize). An intensive effort would be required to estimate the impact of this prize, because its effect on the development of an ALS drug cannot be easily seen. The prize led to the development of a promising biomarker—a potentially useful tool that may increase the productivity of ALS research and drug development—but it has not yet led to the successful development of a breakthrough ALS drug.

Because of limited opportunities to observe complete delinkage mechanisms, like those being developed and beginning to be implemented by DRIVE-AB, it is only appropriate to discuss potential advantages and disadvantages. The primary potential advantage of delinkage is the possibility of achieving a dual aim: achieving dynamic efficiency (the right allocation of resources to long-run R&D goals) and static allocative efficiency (the right allocation of existing drugs to patients) at the same time. Implementing a policy mechanism to achieve this ideal in practice is a difficult task, which is the principal disadvantage of delinkage approaches. Getting the details of the implementation right is a worthy goal, and

it will be interesting for policymakers to observe and learn from the serious effort now being undertaken by DRIVE-AB.

If the limited experience to date with prizes to stimulate drug development shows some promising signs, experience with innovation prizes in other technology fields points to challenges. A case study (Murray et al., 2012) of the Progressive Insurance Automotive XPRIZE, a prize competition cosponsored by the U.S. Department of Energy, found that the types of new technologies sought by innovation prizes frequently require assessment of multiple dimensions of performance, some of which “can neither be quantified nor anticipated, while others may change as the competition unfolds” (p. 1791). Efforts to design and implement prize competitions for drug development may have their greatest chance for success if they are made with full appreciation and understanding of these challenges and the inherent limitations of prize mechanisms. Like with complete delinkage mechanisms, the main advantage is the potential to realize a goal that is eminently sensible in principle; the main disadvantage is the challenge of bringing a good idea to fruition in practice. The example of the ALS biomarker prize—a comparatively small prize, relative to the cost of developing a drug, that can spark new ideas that may prove enormously valuable over the long run—is at least promising, though it may not provide an ideal model, for directly altering incentives for drug development.

7. PRIORITY REVIEW VOUCHERS

A PRV entitles a pharmaceutical company to priority review for a future drug candidate of its choice, shortening review time by about 4 months. A PRV is awarded to a pharmaceutical company at the time of regulatory approval of a qualifying drug or another product. A voucher holder can either use the voucher to speed the review of one of its own drug candidates or, as currently implemented in the United States, sell the voucher to another pharmaceutical company. PRVs are subject to certain conditions, such as advance notice of intent to use the voucher and payment of user fees. PRVs aim to provide a financial incentive to invest in R&D for qualifying products that have low expected financial return by increasing the expected revenues of qualified drug development.

Faster approval has financial value because it accelerates time to market—which can yield both a first-mover advantage for beating competing drugs to the market and time value of money benefit because of earlier sales—and can potentially increase the length of time on the market without generic competition (Ridley and Régnier, 2016). Currently, three U.S. programs—the Neglected Tropical Disease Priority Review Voucher Program, the Rare Pediatric Disease Priority Review Voucher Program, and the Medical Countermeasures Priority Review Voucher Program—reward the development of products in areas of unmet need by providing a PRV. The average selling price for a PRV has been about \$180 million as of August 2017 for 7 PRVs sold.⁸

PRVs have no direct cost to the taxpayer; however, FDA bears administrative expense to provide the priority review when the voucher holder redeems it. Fees that the voucher holder pays to redeem the voucher are intended to offset FDA's administrative expense.

Although representatives of pharmaceutical companies have expressed appreciation for PRV programs and offered anecdotal evidence that these programs have enabled them to develop drugs for diseases they would not otherwise have addressed, the true impact of these programs is unclear at this time. A GAO study of the Rare Pediatric Disease Voucher Program concluded in March 2016 that it was too early to say whether the program had stimulated drug development (GAO, 2016). The 21st Century Cures Act, enacted in December 2016, extended the Rare Pediatric Disease Voucher Program by almost 4 years, authorized a new medical countermeasures PRV program, and required the comptroller general, who heads the GAO, to conduct a study of the "effectiveness and overall impact" of all PRV programs. This report is due to Congress by January 2020.

⁸ Eight PRVs appear to have been sold or transferred as of August 2017. Selling prices (or estimates of selling prices) are available for the 7 PRVs reported to have been sold.

7.1 Background

The two-tiered system of standard review and priority review was introduced in the United States in 1992 by the Prescription Drug User Fee Act. The priority review track is normally reserved by FDA for drug candidates that, if approved, would provide improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition, relative to products already available.⁹ The FDA target for standard review is 10 months. The FDA target for priority review is 6 months. The 10- and 6-month periods are targets, not limits; FDA's goal is to reach a decision within those time frames for at least 90% of applications.

The difference between standard and priority FDA median review times from 2000 to 2006 was 7 months (Grabowski, 2007), but was closer to 4 months in the early 2010s (Ridley and Régnier, 2016). Durations of priority reviews elected by FDA may be shorter than priority reviews compelled by a voucher because applications not eligible for priority review on their own merits may be larger and more complex. They may, for example, be more likely to involve indications for which safe and effective therapies already exist and, therefore, include more extensive trials and patient data (GAO, 2016).

In 2007, Congress authorized the first PRV program in the United States, aimed at spurring development of new treatments for neglected tropical diseases. As originally enacted by the FDA Amendments Act of 2007, medicines for 16 neglected tropical diseases were eligible for a PRV (Table 7-1). Congress added three diseases in December 2014, FDA added Chagas disease and neurocysticercosis in August 2015, and Congress added Zika virus in April 2016.

The FDA Safety and Innovation Act of 2012 created the second PRV program for rare pediatric diseases (those that affect at most 200,000 persons in the United States and primarily affect youth aged 18 or younger). A third, the medical countermeasures PRV program was authorized in December 2016 as part of the 21st Century Cures Act. This program adds voucher eligibility for medicines that prevent or treat "harm from a biological, chemical, radiological, or nuclear agent identified as a material threat" under the Public Health Service Act or as may be later added by Congress or HHS.

Some details of the first two PRV programs were brought into alignment with each other by the 2014 amendments to the Neglected Tropical Disease Voucher Program, called the Adding Ebola to the FDA Priority Review Voucher Program Act (Congress, 2014; Gaffney, 2014). In particular, the notice period to redeem a voucher is now 90 days instead of 1 year, and the fee that a pharmaceutical company must pay FDA to redeem a voucher was

⁹ See <http://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm>.

set at \$2,706,000 for FY 2017.¹⁰ This fee is in addition to any fee normally required for the application. Another change pursuant to the 2014 amendments is that vouchers can be sold an unlimited number of times. The same terms of use apply to vouchers awarded under the medical countermeasures PRV program.

Table 7-1 Voucher-Eligible Neglected Tropical Diseases

| Category | Diseases | | | |
|------------------------------------|-----------------|--------------------|----------------------|--------------------------------|
| Original 16 | Malaria | Blinding trachoma | Buruli ulcer | Cholera |
| | Tuberculosis | Guinea worm | Fascioliasis | Human African trypanosomiasis |
| | Leishmaniasis | Leprosy | Lymphatic filariasis | Soil-transmitted helminthiasis |
| | Schistosomiasis | Onchocerciasis | Yaws | Dengue fever |
| Added by Congress in December 2014 | Cueva virus | Ebola virus | Marburg virus | |
| Added by FDA in August 2015 | Chagas | Neurocysticercosis | | |
| Added by Congress in April 2016 | Zika virus | | | |

Source: <http://www.raps.org/Regulatory-Focus/News/2015/07/02/21722/Regulatory-Explainer-Everything-You-Need-to-Know-About-FDA%E2%80%99s-Priority-Review-Vouchers/>

The rare pediatric PRV program was originally enacted with a sunset of spring 2016, later extended to December 2016, and extended by the 21st Century Cures Act to September 2020. Drug candidates designated for a rare pediatric disease by September 30, 2020, can receive a voucher if approved by September 30, 2022. The medical countermeasures program expires in October 2023. The tropical disease program was enacted without a sunset provision.

As of August 31, 2017, 16 vouchers had been awarded: five for neglected tropical diseases and 11 for rare pediatric diseases (Table 7-2). Publicly available information suggests that six of the vouchers have been sold for a combined value of approximately \$1.2 billion, and one additional voucher was transferred under an agreement predating its award. The selling prices for these vouchers have ranged between \$67 million and \$350 million.

Of the 16 awarded vouchers, nine have not yet been used. However, because we are unable to link one of the vouchers that was recently used to the drug for which it was awarded, Table 7-2 shows 10 vouchers as unused or unaccounted for. The voucher that we are

¹⁰ FDA calculates voucher redemption fees by estimating the incremental cost of conducting a priority review rather than a standard review and then adjusting for the average amount by which FDA's average costs increased in the three years prior (DHHS, 2016).

unable to link back to the original sponsoring pharmaceutical company was used in 2017 by GlaxoSmithKline and ViiV Healthcare. They reportedly acquired a PRV for \$130 million and filed an NDA for a dolutegravir and rilpivirine two-drug regimen for HIV along with the PRV (ViiV Healthcare, June 2017).

Only two vouchers have been used by the original recipients. The first voucher was used in 2011 by Novartis, the original recipient, to speed the FDA's review of canakinumab for gouty arthritis. That indication was rejected. In 2017, Janssen used its PRV to obtain a priority review for Tremfya. FDA approved Janssen's application.

Three other vouchers were purchased and used successfully—all for 2015 submissions. Two additional PRVs have been bought and used on submissions that FDA is currently reviewing. One application is from GlaxoSmithKline and ViiV Healthcare, and the other is from Gilead; both are for new HIV treatment regimens.

Additional detail about each PRV-awarded drug, including information on the indication, development history, and whether the PRV was sold or redeemed, is included in Appendix A.

7.2 Discussion

The PRV concept was originally proposed by Ridley, Grabowski, and Moe (2006) in the context of incentivizing R&D for neglected infectious and parasitic diseases that have public health burden concentrated in low-income countries. In this context, they argued the policy would have dual benefits:

"The priority-review voucher provides two benefits: faster access to blockbuster drugs in developed countries and faster access to cures for infectious diseases in developing countries. There are several reasons to link the benefits. First, the voucher creates a market mechanism that identifies drugs for which priority review would be efficient. Second, the two benefits are more likely to achieve government approval when linked because they appeal to different constituencies" (p. 315).

Although the market mechanism to which Ridley, Grabowski, and Moe refer—the market for tradable PRVs—is likely to identify and allocate PRVs to drugs for which priority review is most valuable to the pharmaceutical companies, they further asserted that the mechanism would identify drugs for which redemption of the priority review voucher would be efficient. In some cases, however, the redemption of priority review vouchers may be inefficient. For example, if a PRV is used for a highly profitable drug that offers modest clinical advantages over other available treatments, then the social value of introducing the drug earlier may be less than the social value of speeding the introduction of a less profitable drug that provides greater public health impact.

Table 7-2. Priority Review Voucher Awards, Transfers, and Uses

| Program | Date | Drug | Disease | Sponsor | Sold ^a | Used ^a |
|-----------------------------|----------|---|---|--|---|--|
| Neglected Tropical Diseases | Apr 2009 | Coartem Tablets (artemether lumefantrine) | Malaria | Novartis | Unsold | Used in 2011 on canakinumab for gouty arthritis (The indication was rejected.) |
| | Dec 2012 | Sirturo (bedaquiline) | Tuberculosis | Janssen Therapeutics | Unsold | Used on Tremfya (guselkumab); approved in July 2017 to treat moderate to severe plaque psoriasis |
| | Mar 2014 | Impavido (miltefosine) | Leishmaniasis | Knight Therapeutics | Sold to Gilead in November 2014 for \$125 million | Used on Odefsey in July 2015; approved in March 2016 as a complete regimen drug for HIV-1 |
| | Jun 2016 | Vaxchora vaccine | Cholera | PaxVax Bermuda | Unknown. Possibly sold to Gilead soon after award for ~\$200 million ^b | Unused/Unknown |
| | Aug 2017 | Benznidazole | Chagas disease in children 2 to 12 years | Chemo Research | Unsold | Unused |
| Rare Pediatric Diseases | Feb 2014 | Vimizim (elosulfase alfa) | Morquio A syndrome | BioMarin Pharmaceutical | Sold to Regeneron and Sanofi in July 2014 for \$67.5 million | Used on the PCSK9-inhibitor alirocumab; approved in July 2015 for the treatment of familial hypercholesterolemia |
| | Mar 2015 | Cholbam (cholic acid) | Rare bile acid synthesis disorders | Retrophin (formerly Asklepios Pharmaceuticals) | Sold to Sanofi in July 2015 for \$245 million | Used in December 2015 on LixiLan, a fixed-ratio combination of lixisenatide and insulin glargine for the treatment of type 2 diabetes; approved in November 2016 |
| | Mar 2015 | Unituxin (dinutuximab) | High-risk neuroblastoma | United Therapeutics | Sold to AbbVie in August 2015 for \$350 million | Unused/Unknown |
| | Sep 2015 | Xuriden (uridine triacetate) | Hereditary orotic aciduria | Wellstat Therapeutics Corporation | Wellstat negotiated a deal in 2014 to transfer the voucher to AstraZeneca upon FDA approval of the drug. Details are undisclosed. | Unused/Unknown |
| | Oct 2015 | Strensiq (asfotase alfa) | Perinatal, infantile, and juvenile-onset hypophosphatasia | Alexion Pharmaceuticals | Unsold | Unused (Alexion stated publicly it plans to use one voucher.) ^c |
| | Dec 2015 | Kanuma (sebelipase alfa) | Lysosomal acid lipase deficiency | Alexion Pharmaceuticals | Unsold | Unused/Unknown |

(continued)

Table 7-2. Priority Review Voucher Awards, Transfers, and Uses (continued)

| Program | Date | Drug | Disease | Sponsor | Sold ^a | Used ^a |
|---------|------------|-----------------------------|---|--------------------------|--|--|
| | Sep 2016 | Exondys 51 (eteplirsen) | Duchenne muscular dystrophy | Sarepta Therapeutics | Sold to Gilead Sciences in February 2017 for \$125 million | Gilead used a PRV in June 2017 for an investigational, fixed-dose combination of bicitegravir and emtricitabine/tenofovir alafenamide to treat HIV. Priority review granted by FDA in August 2017. |
| | Dec 2016 | Spinraza (nusinersen) | Spinal muscular atrophy | Biogen ^d | Unsold | Unused/Unknown |
| | Feb 2017 | Emflaza (deflazacort) | Duchenne muscular dystrophy | Marathon Pharmaceuticals | Unsold | Unused/Unknown |
| | April 2017 | Brineura (cerliponase alfa) | Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) | BioMarin Pharmaceutical | Unsold | Unused/Unknown |
| | Aug 2017 | Kymriah (tisagenlecleucel) | Acute lymphoblastic leukemia in patients up to 25 years | Novartis | Unsold | Unused |

Note: Reflects transfers and uses of vouchers through August 31, 2017, for which publicly available data are available to track the award, sale, and use of the PRV.

^a Reflects all PRVs that are known to have been sold or used and can be linked to the original PRV award. One PRV has been used that is not shown in the "Used" column of the table because the original drug sponsor that was awarded the PRV is unknown. In June 2017, FDA granted priority review in response to a PRV submitted by GlaxoSmithKline and ViiV Healthcare for an HIV treatment regimen (dolutegravir and rilpivirine in a single-tablet form), but the source of the PRV used is unknown (Withers, 2017).

^b Speculation by various sources. See, for example, <https://seekingalpha.com/article/4008098-priority-review-vouchers-revisited>.

^c See <https://pink.pharmamedtechbi.com/PS057234/Priority-Review-Voucher-Not-For-Sale-Alexion-Says-Afterem-Strensiqem-Approval>.

^d Biogen licensed Spinraza from Ionis Pharmaceuticals. As the sponsor, Biogen received the voucher.

Given that PRVs increase revenue after drug approval, like many other policy tools in this report, the incentive effect is much weaker in early stages of drug discovery and development because of the time value of money and the low probability of approval. Yet, PRV programs have received strong support from some in the biopharmaceutical industry (Berman and Radhakrishna, 2017). This support suggests that PRV programs are valuable to pharmaceutical companies, although the programs may not necessarily result in increased investment in targeted disease areas. However, anecdotal evidence from smaller pharmaceutical companies points to an incentive effect: “[T]he prospect of obtaining a PRV is working its way in and impacting [product development partnership] (PDP)-company negotiations and also discussions about the regulatory strategy [...], suggesting that companies do see value in this mechanism” (Berdud, Towse, and Kettler, 2016, 82). David Ridley’s Web site, priorityreviewvoucher.org, highlights testimonials from NanoViricides and Global Health Investment Fund chief executive officers (CEOs), who say that the PRV program influenced their decisions about investing in the development and approval of drugs for neglected tropical diseases. A January 2017 PATH press release credits the Neglected Tropical Disease Voucher Program with attracting investment to drug development projects for dengue, hemorrhagic fever, river blindness, and hookworm.

The recent expansion of PRV programs to include medical countermeasures and the 4-year extension of the Rare Pediatric Disease Priority Review Voucher Program under the 21st Century Cures Act indicates the policy tool’s political popularity. This popularity likely derives in part from the fact that the policy requires no direct financing by taxpayers. Although this feature could be an advantage, it could also make it challenging to eliminate the popular program, even if it was determined that the social costs outweigh social benefits. Although social costs may be difficult to measure, the impact of PRV programs on diverting FDA resources away from drugs with potentially greater public health benefits should be considered in an assessment of PRV programs’ value.

PRV programs have been criticized for rewarding outcomes that could have occurred without the additional incentive of the voucher. Some drugs, like Coartem Tablets (artemether lumefantrine) and Impavido (miltefosine), were awarded vouchers when newly licensed in the United States even though they had been available inexpensively outside the United States for years (Kesselheim, Maggs, and Sarpatwari, 2015). Furthermore, prior to its FDA approval in February 2017, Emflaza (deflazacort) was available in Canada, Europe, and the United Kingdom, and had been imported into the United States for decades by some patients. The high price first announced for its launch in the United States drew the ire of Congressional leaders.¹¹ Kesselheim, Maggs, and Sarpatwari (2015) suggest that this

¹¹ Senator Bernie Sanders and Representative Elijah Cummings wrote a letter to Marathon Pharmaceuticals on February 13, 2017, requesting information about pricing decisions, among other things. (Sanders and Cummings, 2017).

problem could be addressed by requiring pharmaceutical companies to show they had contributed some level of investment to the drug's development to be eligible for a voucher.¹²

The ability of pharmaceutical companies to set high prices for drugs after receiving a voucher because of small patient populations has also led to concerns about patient access. Kesselheim, Maggs, and Sarpatwari (2015) and Ridley and Régnier (2016) suggest adding a requirement that companies provide plans to ensure patient access with their application for the voucher. Ridley and Régnier (2016) further recognize that supplemental policies, like funding from government and foundation sources for the purchase of new medicines for certain populations, may be needed to fully address patient access.

In an interview, then FDA Office of New Drugs Director, John Jenkins, expressed the concern that the user fees paid when a voucher is redeemed may not fully cover the additional staffing needed to conduct the priority review (McCaughan, 2015). On-demand priority review may have real impacts on public health. Providing priority review to a drug candidate that would not be given priority on its own merits "directs time and resources away from other important public health work" (John Jenkins in the same 2015 interview).

Any incentive effect of PRV programs is derived from the expected value of vouchers, which is tied to the price at which one pharmaceutical company can expect to sell the voucher to another. Because the number of high-value new drug launches is limited, the price of vouchers will tend to be lower when more of the vouchers are up for sale at one time. Ridley and Régnier (2016) estimate the magnitude of this dilution effect. In a typical year, if only one voucher were available, it could be expected to sell for \$234 million, whereas if four were available, each might be expected to sell for only \$39 million. This predicted range is roughly consistent with observation. The most a voucher has ever sold for was \$350 million. The second highest price was \$245 million. In February 2017, a voucher sold for \$125 million when as many as six vouchers might have been available to buy.¹³ A reasonable expectation is that anticipation of more vouchers being awarded in the future will tend to diminish the expected present value of vouchers.

The recently added medical countermeasures PRV program may test this dilution effect. In testimony on proposed legislation before the Subcommittee on Health, FDA Director of Strategic Operations in the Office of Counterterrorism and Emerging Threats, Michael Mair, noted that this was already a productive area, averaging more than five medical

¹² Ridley, Grabowski, and Moe (2006) originally proposed that to qualify for the PRV, the therapy would have to be clinically superior to existing treatments, and the sponsoring pharmaceutical company would have to forgo patent rights.

¹³ We cite this as the most recent because it is unclear precisely when a recently redeemed PRV was acquired for \$130 million by GlaxoSmithKline and ViiV Healthcare.

countermeasures per year approved by FDA since 2000 (Mair, 2016). This high rate of drug development could lead to the rapid award of several more PRVs.

With several vouchers unused from the first two PRV programs and the newly enacted medical countermeasures PRV program likely to increase the rate of awards, observation of the trend in PRV prices over the next several years will be instructive. If prices fall as the analysis by Ridley and Régnier (2016) would predict, more attention may focus on how to narrow eligibility for vouchers to preserve their value for cases where PRVs may be especially well suited. Such ideal use cases are unlikely to be characterized by broad disease or therapeutic areas alone.

Many of the drugs that have been awarded vouchers have also qualified for orphan drug exclusivity, pediatric exclusivity, or both. When these drugs are sold in the United States, they can often command high enough prices to generate a sizeable market, even with a relatively small number of patients, and longer exclusivity extends the monopoly rights for branded drugs in that market. In contrast, the PRV is worth the same amount independent of market size of the qualifying drug. This suggests that PRV programs might be best suited to cases where the market is small and, thus, exclusivity extensions have little incentive effect. Eligibility for a PRV could depend on showing that the market is insufficient to provide a return on investment after considering all other incentive programs for which a drug would qualify.

Added incentives are often most needed at earlier stages of development, especially the translational steps from basic science to clinical drug candidate. But because these steps often come dozens of years before an eventual drug approval, when a PRV would be awarded, and because success rates out of these early stages are low, the value of the PRV is discounted more heavily in the drug discovery period. The final value of the voucher itself is also more uncertain several years out, especially considering uncertainty around the number of vouchers that may be awarded in the intervening years. Therefore, PRV programs provide relatively small incentives for earlier-stage research, where the policy imperative is often greatest. However, PRV programs may be well suited to situations where policymakers have an interest in encouraging pharmaceutical companies to conduct Phase III or Phase IV (i.e., postmarketing) trials, where incentives are demonstrably lacking, and where the expected value of the voucher is commensurate with the expected cost of the work to be performed.

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8. WILDCARD EXCLUSIVITY VOUCHERS

A wildcard exclusivity voucher (i.e., exclusivity voucher) would entitle a pharmaceutical company to extend the period of regulatory exclusivity for a product it sells by a fixed amount of time or, if exclusivity vouchers are tradable, to sell the voucher to another pharmaceutical company. A voucher would be awarded to a pharmaceutical company at the time of FDA approval of a qualifying drug.

Like PRVs, exclusivity vouchers are essentially a type of prize, intended to raise the expected return on qualifying R&D projects to attract private investment that otherwise would not have been undertaken. Unlike PRVs, which have been implemented, exclusivity vouchers have only been proposed. Observing how the policy would work in practice is therefore impossible, and the analysis is necessarily more speculative.

In contrast to exclusivity extensions that apply to the drug targeted by the policy, exclusivity vouchers can be applied to any drug marketed by the company or sold to other pharmaceutical companies if the vouchers are tradable. This makes the voucher well-suited to rewarding investment in small-market drugs. Instead of being able to leverage the existing market for only the drug targeted by the policy, the voucher can leverage the existing market of another drug in the company's portfolio—or, if the voucher is saleable, a drug marketed by another company—which greatly increases its potential value.

To get a sense of that potential value, consider that the 10 highest-selling drugs in 2015 ranged in revenue from \$4.6 billion up to \$8.2 billion (Brown, 2015), suggesting that even a 3-month or 6-month extension might be valued at \$1 billion or more. Vouchers awarded in years when more blockbuster drugs are nearing the end of their patent life would be more valuable, because the additional stream of revenue conferred by the voucher begins sooner and is therefore discounted less heavily. Because the number of blockbuster drugs nearing the end of their patent lives at any one time is limited, voucher value is subject to dilution.

Also like PRVs, exclusivity vouchers would impose no direct costs on taxpayers, beyond the costs of administering the program. The voucher's value comes from the additional profits on the sale of the drug for which the voucher is redeemed, which would otherwise have sooner faced competition from generics. Therefore, the cost of the program lands on the patients and payers who bear the higher prices of drugs for which vouchers are redeemed and on the patients who would have taken the drug or a generic equivalent but opt not to take the drug at the higher price. When a voucher is redeemed on a drug heavily targeted to patients with government-sponsored health insurance, such as Medicare or Medicaid, taxpayers will bear the cost indirectly. Some cost is also imposed on generic pharmaceutical companies forced to wait longer to enter large markets.

8.1 Background

Although no exclusivity voucher programs have been implemented, the idea of exclusivity vouchers originated at least as far back as 2000. Kettler (2000a) describes a hypothetical model of “roaming market exclusivity,” in which a number of extra months of marketing exclusivity would be awarded for a specific on-market drug of a company that develops and markets a new drug for a qualifying disease at reasonable price. Ridley, Grabowski, and Moe (2006), citing Kettler, suggest a transferrable patent exclusivity right, whereby a “developer that licenses a product for a neglected disease would receive additional time on patent for a different product, and this right could be sold to another company” (Ridley, Grabowski, & Moe, 2006, p. 317).

Proposed legislation in the United States also goes as far back as 2000. A draft in 2000 of the U.S. Drug Demand Reduction Bill, which sought to encourage the development of new drugs for treating dependence on a controlled substance, included a provision that was not passed for offering extended market exclusivity rights to an unrelated on-market drug (Kettler, 2000b). A U.S. Senate bill cosponsored by Senators Joseph Lieberman and Orrin Hatch in 2005 proposed wildcard exclusivity to reward pharmaceutical companies that successfully develop a biodefense countermeasure; vowing to oppose the bill, Henry Waxman called it a “misguided giveaway to the brand drug industry” (Meland, 2005).

Exclusivity vouchers have attracted recent attention from policy advisors and legislators. Tradable vouchers received a limited, cautious endorsement as an approach to encourage the development of antibiotics from the President’s Council of Advisors on Science and Technology in 2014 (PCAST, 2014). In September 2015, Senator Robert Casey introduced a bill “to promote the development of safe drugs for neonates” (S. 2041, 2015, pp. 1). The bill would award a transferrable voucher, good for a 1-year extension of all patents and marketing exclusivities, for a single drug or biologic product on approval of a neonatal drug application. The voucher program proposed in the bill, which has not become law, would require notice of intent to redeem a voucher 15 months prior to patent expiration and would require transfer of a voucher to be reported to the Secretary of HHS by its new owner within 30 days.

8.2 Discussion

Like PRVs, exclusivity vouchers are a novel reward mechanism that could be part of an otherwise well-designed delinkage model. They have the key advantage of providing a large incentive for later stage development to encourage drug development that is especially costly, lengthy, risky, and/or expected to result in small revenues from the drug. Because of this, exclusivity vouchers may be most appropriate when the private hurdle rate is very high and private expected revenues are close to zero (Figure 1-1).

Exclusivity voucher programs redistribute net benefits. For the voucher programs envisioned by Kettler (2000a) and Ridley, Grabowski, and Moe (2006), this was a desirable feature: delivering the benefit of new medicines to patients in lower-income countries and placing the cost on the relatively wealthy patients and payers in higher-income countries. Even in such a Robin Hood scenario, redistribution is typically a contentious issue. It could be more of an issue if exclusivity voucher programs are proposed to target unmet medical needs in the United States, so that different U.S. interest groups are placed at odds. “Public health advocates, for example, may ask why patients taking a statin drug (or their insurers) should bear the financial burden of incentivizing antibiotic development” (PCAST, 2014, p. 40).

Because their value depends on the sales of profitable drugs, no direct appropriation is required to support exclusivity vouchers. Although this feature may lower political barriers to implementing a well-designed voucher program, it also lowers barriers to implementing a mistargeted program. What is more, if a program was implemented on a trial basis, with a requirement for review and a sunset provision, as with some PRV programs, the fact that it requires no direct appropriation might make it more likely that even a program found to be working poorly would be reauthorized.

In comparison to a set reward for achieving specified drug development criteria, exclusivity vouchers provide an award that may be larger than the amount necessary to incentivize development of a given type of needed drug. In principle, the expected value of the voucher could be controlled by adjusting the number of months of additional exclusivity (e.g., a single month might be an appropriately sized reward). However, Senator Casey’s proposal in September 2015 of a 1-year exclusivity extension voucher suggests at least the potential for imperfect legislation to implement overly generous rewards. Consider the example of “a mature blockbuster drug with \$4 billion in annual sales,” for which even just “a three-month extension would yield \$1 billion in additional sales—corresponding to profits of \$800 million, assuming margins on a mature drug of 80%” (PCAST, 2014, p. 40).

The costs of exclusivity vouchers are borne by patients and payers, but predicting in advance which patients would be affected and how is not possible. The cost depends on which generic products are delayed when a voucher is redeemed. Extending a patent likely would be costlier than extending regulatory exclusivity because patents afford brand name pharmaceutical companies a larger set of avenues to deny generics entry. For example, provisions in U.S. patent law block the marketing of generics if the brand name company alleges that one or more of the patents on the originator product is still valid; this action can delay marketing of the first generic by up to 30 months.

Like PRVs, exclusivity vouchers could conceivably be used to promote the development of new drugs targeting any therapeutic area. But if we want to award a small number of exclusivity vouchers, it may be challenging to effectively establish and monitor the public health priority, or set of priorities, to target with additional incentives. Also like PRVs,

exclusivity vouchers that are tradable may be especially attractive to incentivize drug development among smaller companies because the expected value of the exclusivity voucher may be sufficient to drive investment at all stages. That is, a 3- to 6-month exclusivity extension on a blockbuster drug could present such a large prize that it could spur a pharmaceutical company to undertake even early-stage research, with all the discounting of the future reward that implies (discounting for the risk of failure at some point before successful launch of a new drug and discounting for the time value of money).

One challenge in targeting early-stage research with a prize (the exclusivity voucher in this case) to be awarded at the time of marketing approval—even when the prize is large enough for that purpose—is establishing criteria that prevent such a large prize being awarded for a drug that was already in the later stages of development when the prize was offered. Such awards are unlikely to have influenced the company's decision-making in the ways intended by policymakers. In theory, an exclusivity voucher program could require pharmaceutical companies to register their R&D projects to qualify for the program, making companies that register at earlier stages eligible for longer extensions (in voucher form). However, this idea would be challenging to implement. In addition to establishing criteria for which newly approved drugs would qualify for a voucher, serious thought would be needed to determine the appropriate size of the incentive offered to projects that had already progressed to different stages of development without any added incentive. Other challenges would be assembling an appropriate group of administrators from different federal agencies to oversee such a nuanced policy and getting pharmaceutical companies to participate in the registry, because of concerns that their confidential and proprietary information could be exposed.

Without this kind of nuance in the policy implementation, the most likely outcomes would be either a small prize (i.e., a relatively short exclusivity extension in voucher form) that can be expected to incentivize later-stage development of projects that have attracted enough public and private investment to progress that far or a larger prize (i.e., a longer exclusivity extension in voucher form) that may be sufficient to attract private investment to some earlier-stage R&D efforts but that may also provide large profits to some drugs already in later stages of development.

9. ADVANCE MARKET COMMITMENTS

Advance market commitments (AMCs) are agreements to fully or partially finance the purchase of a specified amount of a medical product at a pre-arranged price, prior to its development. In an AMC, a program sponsor or coalition of investors agrees to a contract stipulating a price for the product (e.g., \$15 per unit) for a fixed quantity of the product. The final customer will then purchase the product at a steeply discounted price (e.g., \$1 per unit). Once the agreed-upon amount of the product is sold, the developer may either continue selling the product at an affordable price or license it out to other pharmaceutical companies (Berndt et al., 2007). If the product is not developed, no subsidy is provided. AMCs are considered a delinkage mechanism because they provide a fixed amount of revenue to the producer, regardless of how much of the product is sold to consumers.

First proposed in the context of encouraging the development of vaccines for developing countries (Kremer, 2000a, 2000b), the guiding principle of an AMC is to spur private investment in drugs through the creation of markets by a credible commitment to subsidize their purchase once they are developed (Tremonti, 2005). The mechanism through which AMCs are designed to incentivize investment is de-risking the revenue associated with the drug. The subsidy typically specifies the price per dose, the number of doses for which that price will be paid, and the timing of those purchases. Once the subsidy runs out, the product is then offered at a low or fair price (marginal cost of production). AMCs are not winner-takes-all and can be divided up among drug developers. If designed particularly well, they can encourage subsequent market entrants with superior, more effective drugs.

AMCs are intended to address the time-inconsistency problem of drug development. Some biomedical products—of which vaccines are a prominent example—can be manufactured at a relatively low cost in relation to the R&D time and costs needed to bring them to market. When the purchasers of the product, often low income countries, wield substantial market power, once a company has undergone the R&D to develop a product, purchasers may demand that the product be priced at the marginal cost of production (Berndt et al., 2007; Levine, Kremer, and Albright, 2005). If companies know that purchasers will pursue this goal, they will underinvest in R&D and will not develop new products to treat populations because they cannot recoup the R&D costs. Therefore, to spur investment, returns provided by an AMC must equal that provided by diseases affecting a larger population with a greater willingness to pay (Tetteh, 2012). For a product that is already in the later stages of development, a firm will continue investment through launch of the drug if expected returns are sufficient to cover the costs of production.

9.1 Background

An AMC requires three key elements: detailed product specifications, estimates of prices and market sizes, and a credible commitment. First, to ensure that the purchaser is

receiving an effective product, it needs to set minimum specifications for medical effectiveness. This needs to be done with the initial entrant into the market to ensure that the product is safe for use and effective at treating the disease. The purchaser may decide to contract with an independent third party for tests of drug safety and efficacy. Specifications also need to be set as to what constitutes a legitimate second drug entry into the market. A balance must be struck to encourage secondary market entrants, but also to hinder the development of products structurally similar to the incumbent with only minor differences. Berndt et al. (2007) and Levine, Kremer, and Albright (2005) recommend following the clinical superiority clause in the U.S. Orphan Drug Act.

Second, an incorrect price or market size calculation could be problematic for AMC implementation; too high a price will lead to a waste of public resources, while too low a price will not encourage enough investment for the development of new product (Towse & Kettler, 2005). AMC pricing requires that the funder have knowledge of both the market for the drug and the regulatory environment in which it is being developed to account for the risk in developing the product. A system set up to reward the incremental improvements in health, such as value-based pricing, may be able to account for this risk (Stiglitz and Jayadev, 2010). The developer and funder must also agree to a long-term price that reflects the marginal costs of production, also known as the tail-end price. This price would go into effect after the AMC funding is depleted. Prices for second and subsequent market entrants need to be considered as well. Later-stage products would necessitate smaller market size commitments, reflecting the lower level of risk in development. Levine, Kremer, and Albright (2005) suggest a market commitment comparable to the net present value of revenues for a new chemical identity.

Finally, private firms must believe that the supporters, either government or private entities, or some combination, of the AMC will still honor a signed agreement years into the future, when the product has been developed. Even if the full AMC amount does not ultimately have to be paid, the funding must be credible. For a United Kingdom AMC that encouraged the development of a meningitis vaccine, the government repeatedly made public statements to reassure developers that the government would honor its commitment to purchase the vaccine at the end of the process (Towse & Kettler, 2005). Regardless of the exact amount of funding required, an explicit financial commitment is required (Levine et al., 2005).

Several variants of AMC agreements have been tried. The pneumococcal vaccine program launched in February 2007 by various governments and funders involved a technical specification whereby suitable products, nearly fully developed, were identified in the pipelines of two pharmaceutical companies, GSK and Pfizer. Both companies' vaccines were then approved and being manufactured by 2010. Although the target was 200 million doses annually by 2015, GSK and Pfizer each agreed to supply 30 million doses annually for 10 years, beginning in 2013 (with additional doses supplied in 2010, 2011, and 2012). Each

company agreed to supply 15% of the full targeted supply in exchange for 15% of the \$1.5 billion fund. Another successful AMC agreement was conducted by the United Kingdom government in creating a meningitis C vaccine. The meningitis C vaccine arrangement involved three pharmaceutical companies who had early-stage meningitis C vaccines already developed and each were promised a share of the UK market. No formal contracting occurred and this arrangement lacked the hallmark two-tiered pricing system. Two AMCs for malaria and AIDS vaccines have been proposed: one by the Centre for Global Development (CGD) in 2005 and another by the Malaria Vaccine Initiative in 2006. Currently, no vaccines have been developed for either malaria or AIDS under these programs.

9.2 Discussion

By providing an upfront subsidy for completed production, AMCs are a type of delinkage mechanism. Compared to other delinkage mechanisms and policy tools designed to incentivize investment in R&D, AMCs are structured to target a market as a whole rather than a specific product. Unlike many policy tools, AMCs are not winner-takes-all. Properly designed AMCs can and should allow for secondary (and tertiary) market entrants, assuming they are deemed clinically superior to the primary entrants. Promoting market entrants is best accomplished through guaranteeing a market, rather than through promising an increase in revenue after approval, as is the case with other policy tools, such as priority review vouchers (PRVs) and prize funds.

Designing an effective AMC necessitates a tremendous amount of foresight on the parts of both the purchaser and the pharmaceutical company, who must forecast the product specifications and expected payouts for a market into the future, mitigating as much risk as possible. AMCs require a precise product specification to ensure that contracting conditions are met. The product specifications may be set by an independent authority and have been established through clear and transparent decision making. Uncertainty as to the final product specification could deter pharmaceutical companies from investing in R&D. Given this uncertainty, AMCs may be more effective when there is an existing base of science and knowledge to draw from. A poor forecast of market demand could result in wasted taxpayer dollars or a lack of a sufficient subsidy. If an incorrect market forecast is given, the government may be less able to change direction in response to a shifting market than a private firm would be. As a rough proxy for determining the size of a market needed to attract private investment, Levine et al. (2005) used the sales of 118 new medicines introduced in the United States between 1990 and 1994. They found that the present value of lifetime sales revenues for these products was \$3.1 billion (in 2004 dollars). Levine et al. then looked at malaria endemic to Africa and estimated that the commercial market in the absence of an AMC was roughly \$850 million. Therefore, to create a market on par with the average new medicine, an AMC would need to be valued at \$2.3 billion.

The intrinsic design characteristics of an AMC are critical and represent a challenge for policymakers. Design features such as a subsidy cap tied to the supply commitment of each firm do not matter when there are multiple competitors in the market, but do matter a great deal if there is only a single supplier in the market (Snyder et al., 2011). A subsidy cap should specify that a firm could only earn the proportion of the AMC fund that was supplied. As described by Snyder et al. (2011), this design element, which was missing in the original concept of the program and was added after the program's inception, was critical to the success of the pneumococcal AMC program. In the absence of competition and a subsidy cap, a pharmaceutical company could constrain the buildout of capacity and possibly earn the entire AMC fund over a longer timeframe, while supplying a suboptimal annual supply of products. Therefore, if an AMC is not carefully designed, it will provide a suboptimal level of production from a societal standpoint.

The characteristics of AMCs that made them particularly applicable to the meningitis C or pneumococcal vaccine also highlight their narrow applicability, especially within the U.S. context. The purchaser or purchasers must possess substantial market power. In the absence of market power, such as in the United States where multiple purchasers exist and pharmaceutical companies typically have bargaining power, companies are unlikely to reduce price after the product's development. For vaccines, however, purchasers have typically been low-income countries in control of much the demand and able to extract lower prices from pharmaceutical companies. Additionally, the product itself must require substantial R&D costs yet have a low marginal cost of production. The purchaser must know that the costs of production are structured this way. The pharmaceutical company will therefore be unwilling to commit to R&D because of concerns that the purchaser will try to renegotiate after development. These characteristics limit the set of products and the context to which AMCs could be applied.

AMCs' social benefits are illustrated in Figure 10-1. Because of the high social return but relatively low private return of developing products such as vaccines that target diseases commonly found in developing countries, point A represents an ideal project for an AMC program to target. The private hurdle represents the small market in developing countries that, on its own, is insufficient to incentivize investment in R&D in these vaccines. An AMC could yield a high potential social return by guaranteeing a price and boosting the private return from A to A'. For example, the conjugate vaccines for meningitis C imparted substantial social returns because they led to higher levels of herd immunity than originally expected (Maiden et al., 2008).

An additional benefit of the two-tiered pricing scheme is that, after the predetermined quantity is sold at the specified higher price, the developer could be legally required to continue selling the drug at a more affordable price than paid out as part of the AMC or to license the drug out to other pharmaceutical companies to sell at a lower price (Berndt et al., 2007). This pricing structure could therefore result in a sustainable long-term market,

which could improve drug access and health outcomes. AMCs may provide further social benefits by accelerating the diffusion of existing or late-stage-of-development drugs to developing countries. For example, evidence suggests that the AMC for pneumococcal vaccines resulted in a more rapid dispersion of the second-generation vaccines in the developing world than would have happened under regular market conditions (Snyder et al., 2011). As a result, AMCs have been indicated as a key tool to enhance access to vaccines for neglected diseases primarily affecting poor countries (Kremer & Williams, 2010).

AMCs function best when targeted at products already in later stages of R&D, which reduces uncertainty in estimating market size and product specifications. Although in theory AMCs are possible for early-stage development—in fact, Levine et al. (2005) consider an AMC for early-stage development of a vaccine for malaria—AMCs have historically been targeted at drugs in later stages of development likely because product specification and market size calculations are more easily obtainable in later stages. AMCs for basic research are challenging, if almost impossible, to specify (Kremer, 2000a). Furthermore, even if well specified, AMCs as currently envisioned (absent milestone-based payments) would have less of an incentive effect in earlier stages due to the time value of money and the relatively high probability of failure of drugs early in development. Thus, AMCs may be most appropriate when complemented by other “push” policy tools that spur early-stage development such as funding for basic research and product development or when a viable product has reached later stages of development but is not commercially viable in the absence of an AMC. Tremonti (2005) states that “Because [AMCs] increase the probability that the results of public research will be picked up and translated into products that are actually used, AMCs complement, and do not substitute for, other policies to support R&D on diseases concentrated in poor countries” (p. 4).

To take full advantage of the rewards the AMC offers, a pharmaceutical company must be able to not only develop and gain FDA approval for the drug, but also to produce the drug itself. Without the physical product, no reward is provided. As such, AMCs favor large multinational pharmaceutical companies that can obtain approval for the drug and have the capacity to supply it to foreign nations. For example, only two large multinational firms, GSK and Pfizer, were able to supply the 30 million doses of pneumococcal vaccine needed annually for 10 years, beginning in 2013, with additional doses to be provided in 2010, 2011, and 2012 during ramp-up (Snyder et al., 2011).

The contexts and therapeutic areas that are best suited for an AMC differ from those best suited for other policy tools because of this critical distinction between increasing revenue and guaranteeing a market. AMCs are best suited for therapeutic areas with a straightforward need for a product, given the challenges associated with identifying and enumerating the technical specifications of a program. In theory, AMCs were first designed for use in the vaccine market, because they provide large social benefits (Kremer, 2000a,

2000b). In practice, their usefulness as a policy tool has suffered as a result of their narrow applicability.

10. AN ILLUSTRATIVE ANALYSIS: A CLOSER LOOK AT PRIORITY REVIEW VOUCHERS

This section provides a deeper analysis of PRVs, examining more closely several issues touched on in Section 7: inherent difficulties in targeting vouchers effectively, the potential for dilution of voucher value as voucher programs expand or proliferate, and the sensitivity of vouchers' incentive effect to development cost across successive stages of development.

10.1 Targeting

A policy tool that is effective at targeting will attract needed public health investment, rather than providing a windfall to pharmaceutical companies at a cost to consumer welfare for drugs that would have been developed even in the absence of the tool. Thus, a policy tool succeeds if it leads to the development of new drugs with positive expected net social value—the value to individual patients and to public health that exceeds the cost of development including the cost of the public policy interventions. For PRVs, their success at targeting depends on properly setting the criteria for voucher awards that result in positive net social value. Figure 10-1 illustrates this idea, focusing on the potential effect of a PRV's having expected value V to a pharmaceutical company considering undertaking an R&D project to produce a new PRV-eligible drug.

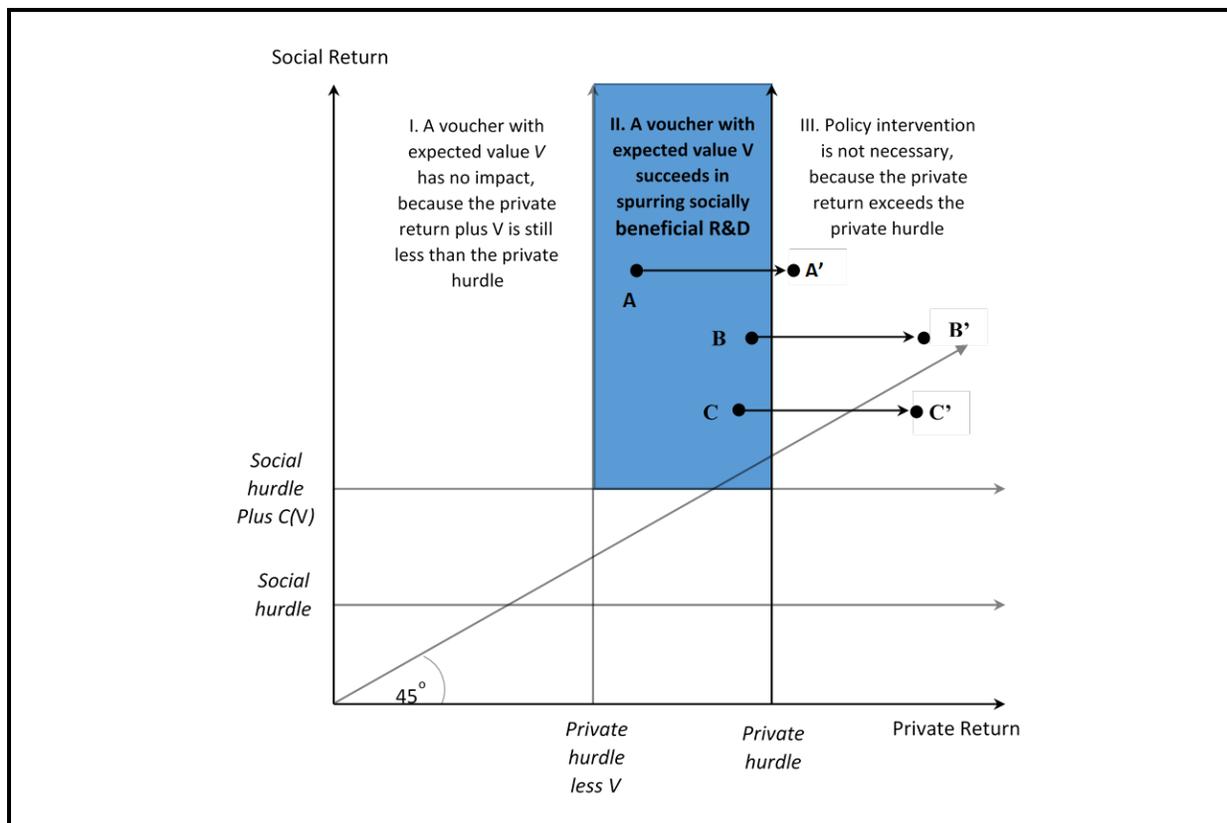
The horizontal axis in Figure 10-1 measures the expected private return on R&D investment—the expected present value of the stream of profits that accrue to the pharmaceutical company that successfully sponsors the new drug resulting from the R&D. The vertical axis measures the expected social return on that investment—the expected present value of the stream of benefits, including the full public health benefits of the new drug.

The private and social hurdles are the required private and social returns on R&D investment. The required returns are the present-valued private and social costs of performing the R&D, plus an adequate return on investment, considering the risk of failing to develop a drug and obtain marketing approval. It is usually reasonable to think that the private hurdle should be greater than the social hurdle. One reason is that the opportunity cost of public investment capital is typically lower than that of private investment capital. Therefore, the private and social hurdle lines intersect below the 45-degree line. Note that policy intervention is ideally focused in the region above the 45-degree line, where the social spillover is large and social return exceeds the private return.

The potential for successful impact of a PRV program is seen in Region II (shaded). In this region, the R&D is socially productive; the social return exceeds the social hurdle accounting for the social opportunity cost of the voucher, $C(V)$. The R&D project would not have attracted private investment without the voucher, because the private return is less than

the private hurdle. When the voucher's value is added to the private return, this combined value exceeds the private hurdle, and the R&D will be able to attract private investment.

Figure 10-1. Conceptualization of a Successful Policy Intervention



Notes: The PRV has expected value V to a pharmaceutical company considering a drug R&D project. The social opportunity cost of the voucher is $C(V)$. The blue shading indicates the region (Region II) in which a PRV would succeed in spurring socially beneficial R&D. In Region I, the voucher would have no effect because the expected private return, even after adding the expected value of the voucher, is still less than the private hurdle, which is the expected cost of the R&D that would realize that return. In region III, the voucher would have no effect because the private return is greater than the private hurdle even without the voucher. In the favorable Region II, project A is an ideal target for the PRV in two important respects: its social return is much greater than its private return (i.e., the social spillover value is large), and almost all of the voucher's expected value is needed to clear the private hurdle (by moving from the point A to the point A'). Project B is less ideal; although the social spillover is still large, the private value is close to the private hurdle, meaning that most of the voucher's expected value is not actually needed to clear the hurdle. Project C has a smaller spillover (point C is closer to the 45-degree line), so small that the private return together with the voucher value is actually greater than the social value of the drug for which the voucher was awarded (as seen because the point C' is below the 45-degree line). The figure is adapted from Jaffe (1998).

One size advantage of PRV programs over alternative policy interventions may be understood in terms of how PRVs can enlarge Region II in Figure 10-1. The magnitude of a PRV is represented in the figure by the width of Region II. Recipients have sold their vouchers for between \$67.5 million and \$350 million. These values are an order of

magnitude larger than the largest prizes offered through prize competitions by U.S. federal agencies with their expanded authority under the America COMPETES Reauthorization Act of 2010.¹⁴ This suggests that vouchers may help to overcome limitations in the amounts of more conventional prizes federal agencies may be able to offer.

A second potential advantage of PRV programs is their ability to offer large prize incentives at low cost by leveraging the difference between the willingness of pharmaceutical companies to pay for priority review of a drug candidate of their choice and the social opportunity cost of providing the priority review on demand, thus minimizing $C(V)$. Although it is true that vouchers do not require a direct appropriation from the discretionary budget of any federal agency (as would a prize paid outright), this does not necessarily imply low social opportunity cost. In statements to the GAO, FDA officials have expressed concern that having to provide priority reviews of drug candidates that do not meet the usual standard for priority designation “adversely affects the agency’s ability to set its public health priorities” (GAO, 2016). In an earlier interview, FDA Office of New Drugs Director John Jenkins expressed the concern that the user fees paid when a voucher is redeemed “do not translate to additional staffing to support the division that must conduct the priority voucher review. The time required to hire and train additional review staff is much longer than the ‘lead time’ in which FDA receives the additional fee revenue, and the additional fees collected are not designed to support the additional staff time beyond completion of the first-cycle review. It is not logical or feasible for FDA to recruit and train staff only to be forced to let them go once the acute project is completed.”¹⁵ Given this, on-demand priority review may, in fact, have real impacts on public health. Providing priority review to a drug candidate that would not be given priority on its own merits “has the adverse impact of requiring managers and reviewers to refocus time and resources away from other important public health work, such as reviewing other applications for potentially much more serious conditions or drafting of guidance documents on issues related to drug development” (John Jenkins in the same 2015 interview). It is also conceivable that the earlier approval of some of the drugs using priority review vouchers will involve a social cost, in cases where the social value of the drug is less than the price the company can charge.

Another potential advantage of PRV programs is that the FDA may find it feasible to commit to awarding a voucher at an uncertain date more than several years in the future in a way that the FDA or another federal agency would find it difficult to commit to paying such a

¹⁴ Section 105 of the Reauthorization Act (Public Law 111-358) expanded federal agencies’ authority to offer prizes by amending the Stevenson-Wydler Technology Innovation Act of 1980, adding Section 24 (Prize Competitions), <https://www.gpo.gov/fdsys/pkg/PLAW-111publ358/pdf/PLAW-111publ358.pdf>. For details, see <https://www.challenge.gov/list/> and sort in descending order of prize amount. The largest of these is the \$20 million Antimicrobial Resistance Rapid Point of Care Diagnostic Test Challenge.

¹⁵ See <https://pink.pharmaintelligence.informa.com/PS079786/FDAs-Concerns-With-PRVs>.

large prize out of its discretionary budget. This is a desirable feature given the length of time between preclinical studies and submission of a New Drug Application (NDA) or Biologics License Application (BLA). This advantage is undermined if PRV programs are authorized for only short periods. With reauthorization required every two years, a pharmaceutical company considering preclinical development of a qualifying drug will need to consider the chances that the program is reauthorized four or five times so that the voucher will be available when and if it reaches NDA submission. The expected future value of a voucher for one set of qualifying drugs may also be affected by the chances of other voucher programs being introduced and the vouchers awarded under those other programs, when they are put up for sale, diluting the market value of each voucher. Therefore, being able to commit to award a voucher is not the same as being able to commit to award a certain value.

Some potential pitfalls can also be understood from Figure 10-1. In Region I, a voucher with expected value V has no impact because the private return plus V is still less than the private hurdle. There is no direct cost to awarding vouchers in this region, because eligible R&D projects are not undertaken (eligible drugs will not be developed) and so no vouchers are awarded, but if most eligible projects are concentrated in this region, the PRV program will be less effective; there simply will not be very many projects that can attract private investment, even with the hope of obtaining a voucher. In Region III, the voucher has no impact because these projects would have been undertaken in any case. For reasons that will be explained in more detail below, if many eligible projects are concentrated in Region III, both main advantages of PRVs are undermined: the effectiveness of the PRV program will suffer, because V will be reduced, and the cost of the PRV program will probably increase, because $C(V)$ will be increased (especially through greater constraints imposed on the FDA's ability to set its public health priorities).

In the favorable Region II, project A is an ideal target for a PRV program in two important respects: its social return is much greater than its private return (i.e., the social spillover value is large), and almost all the voucher's expected value is needed to clear the private hurdle. Project B is less ideal. Although the social spillover is still large, the private value is close to the private hurdle, meaning that most of the voucher's expected value is not actually needed to clear the hurdle. Project C has a smaller spillover, so small that the private return together with the voucher value is actually greater than the social value of the drug for which the voucher was awarded (as can be seen because the point C' is below the 45-degree line). We will discuss some reasons why it may be useful to minimize instances of awards to projects like B and C.

Figure 10-1 also illustrates that awarding vouchers to drugs for which the social value is less than the social hurdle plus the opportunity cost $C(V)$ reduces social welfare. A voucher program that effectively minimizes instances of awards to such drugs and to drugs in Region III of Figure 10-1, and concentrates most voucher awards on Region II (especially

on projects well described by the point A), is said to be well targeted. From the discussion in Section 7, it is not obvious that any of the drugs that have been awarded PRVs to date have been Region-II drugs, and it seems especially unlikely that any have been Project-A types.

Several potential disadvantages of PRV programs should be considered. First, recognizing the importance of targeting voucher awards, an important question is whether specific PRV programs are effectively targeted and whether PRV programs in general may face inherent obstacles to effective targeting. One feature of PRV programs, and a potential source of such obstacles, is that the size of the award cannot be directly controlled or tied to either the value of a drug candidate or the amount of additional incentive needed to attract the private investment necessary for its development. Therefore, because the program offers the same reward for all qualifying products, a voucher, there is no incremental benefit to pursue harder R&D problems with potentially greater social benefit. Instead, firms will select the lowest-cost pathways to secure an equal or greater chance at a voucher. Targeting will always be an issue unless the policy targets diseases very strategically or includes some forward-looking assessment of the potential social benefit.

Another potential disadvantage, related to having no direct control over the expected value of the voucher, is that the award cannot be broken up and paid out in parts (or staged), with each payment tied to successful completion of a milestone. Related to these potential disadvantages is the uncertainty of the value of the voucher, and that the uncertainty is not tied to the social value of the new drug.

PRV program administrators also have limited control over the distribution of who receives the value of the voucher. The voucher is awarded to the pharmaceutical company that successfully sponsors a qualifying drug; this company may or may not have made significant contributions to the drug's development. Larger pharmaceutical companies may typically be able to extract larger rewards from vouchers, by virtue of their superior bargaining position when acquiring a drug candidate from a smaller company and when exchanging a voucher (either selling a voucher that was awarded to them or buying a voucher from the awardee). On the other hand, while larger pharmaceutical companies may be positioned to realize some share of the PRV value in these scenarios, the value of the PRV is likely to be factored into the acquisition price demanded by and paid to smaller firms.

Because the PRV is awarded at the time a new drug is approved, the PRV is not ideally suited to address issues related to patient access (especially relevant for neglected diseases of the developing world) and rational use¹⁶ (relevant for antibiotics). When such issues are

¹⁶ Rational use of medicines means that patients receive appropriate medications, dosing, and treatment periods to meet their clinical needs at the lowest social cost (WHO, 2012). Antibiotic markets, for example, suffer from irrational overuse that exacts a social cost by increasing antibiotic resistance.

relevant and it is not possible to address them with complementary policy interventions, such as patent buyouts, the social value of developing a new drug (even a very good drug) may be very low, and so a PRV program to spur drug development in such situations may be ineffective, essentially because of the lack of many eligible R&D projects like Project A in region II of Figure 10-1.

These potential advantages, associated caveats, and potential disadvantages are summarized in Table 10-1.

Table 10-1. Potential Advantages and Disadvantages of PRV Programs

| Advantages | Caveats | Disadvantages |
|---|--|---|
| <p>PRV programs may enable administrators to provide relatively large rewards for successful development of qualifying drugs.</p> <p>PRV programs may enable administrators to provide potentially large rewards at relatively low social cost.</p> | <p>If awards are not well targeted, vouchers may over-reward modest incremental (typically late-stage) drug development efforts or drugs that would have been developed in any case; this may reduce the expected value of vouchers and increase their social opportunity cost.</p> <p>In contrast to a prize in the form of a direct appropriation, which has a straightforward direct cost, PRV programs have a number of indirect costs such as potentially diverting FDA resources away from drugs with potentially greater public health impact, making the actual social opportunity cost difficult to assess.</p> | <ul style="list-style-type: none"> ▪ PRV awards may be inherently difficult to scale effectively; the amount of the award cannot be directly controlled and so cannot be tailored to the social value of a specific drug or to the incremental incentive needed for the drug to be developed. ▪ PRV awards cannot be broken up and paid out in parts (staged) with each payment tied to successful completion of a milestone. ▪ The value of a voucher is highly uncertain, and this uncertainty is in no way tied to the social value of the new drug. ▪ Voucher recipients (companies that successfully sponsor qualifying new drugs) may or may not have made significant contributions to the drug’s development. There has been some evidence of gaming the system in the United States. ▪ Vouchers may disproportionately reward larger companies that are more likely to be able to (1) acquire qualifying drug candidates from smaller companies on favorable terms and (2) buy or sell vouchers on favorable terms. ▪ PRV programs are poorly suited to address issues of patient access and rational use; when these issues are relevant, PRV programs may be ineffective without complementary policies, such as patent buyouts. |

(continued)

Table 10-1. Potential Advantages and Disadvantages of PRV Programs (continued)

| Advantages | Caveats | Disadvantages |
|---|---|---------------|
| <p>PRV programs enable administrators to provide potentially large awards at uncertain dates more than several years in the future, which is difficult to credibly do with other policy mechanisms that require a direct appropriation.</p> | <p>PRV programs that must be reauthorized frequently exacerbate uncertainty for administrators and private pharmaceutical companies alike. Also, the expansion of PRV programs into additional areas, to the extent it increases the expected number of vouchers awarded and outstanding at a given time, potentially dilutes the market value of vouchers; therefore, commitment to awarding a voucher is not the same as commitment that its value will be at least a given amount.</p> | |

10.2 Dilution of Voucher Value

The incentive effect of a PRV is directly tied to the expected value a pharmaceutical company attaches to the voucher they hope to obtain. As with other goods, if the supply of vouchers is increased via additional PRV programs more than the rate of NDA submissions for probable blockbuster drugs, a reasonable expectation is that the market value of the vouchers will decline, diminishing the incentive perceived by a pharmaceutical company hoping to obtain and sell a voucher in the future. Policymakers should be concerned with the value of the vouchers diluting as the number of vouchers in circulation rises. Our analysis adds to existing work by Ridley and Régnier (2016) and Robertson, Stefanakis, and Joseph (2012) by providing a quantification of the link between the supply of vouchers and the impact on their value.

Pharmaceutical companies awarded vouchers will typically prefer to sell the voucher rather than redeem it on a drug in their own pipeline. Intuitively, this is simply because the chances are small that a company awarded a PRV will also happen to have in its pipeline one of the several biggest prospective blockbuster drugs nearing NDA or BLA. In a survey of industry executives of pharmaceutical companies with active drug or vaccine R&D programs for PRV-eligible diseases, Robertson, Stefanakis, and Joseph (2012) find that the average expected price of selling a PRV was roughly twice the price a company would be willing to pay to obtain a PRV for itself. Furthermore, of the PRVs that have been redeemed to date, only two were redeemed by the original awardees.

The most comprehensive and most recent study of voucher values, Ridley and Régnier (2016), considered drugs approved by FDA between January 1, 2007, and December 31, 2009. In their baseline scenario, with an average of 4 months' faster approval and assuming

average 5th-year sales of \$914 million, the value of the voucher was \$234 million (Table 10-2). Robertson, Stefanakis, and Joseph (2012) found a similar value.

This \$234 million is an estimate of the most any company would be willing to pay for one available voucher in a given year (the company’s reservation price), which is more than the price at which a company would typically expect to sell a voucher. A pharmaceutical company could sell a voucher for the buyer’s reservation price only if they, the seller, had an unrealistically strong bargaining position. Also, note (in Table 10-2) that \$234 million is the middle of a wide range: \$45 million to \$657 million from Ridley and Régnier (2016) or \$56 million to \$303 million from Robertson, Stefanakis, and Joseph (2012).

To capture the dilution effect, we modeled dilution per the demand curve outlined in Exhibit 4 of Ridley and Régnier (2016). One approach would be to focus on the midpoint between the value to the buyer and the value to the alternative buyer (see Figure 10-1). The alternative buyer is the buyer with the next-highest willingness to pay (the second highest if one voucher is outstanding, the third highest if two vouchers are outstanding, and so on). If the buyer and seller have roughly equal bargaining power, they might agree to split the difference between the buyer’s willingness to pay and a reasonable guess at the next-highest willingness to pay, which serves as the seller’s reservation price. This may overestimate the likely selling price somewhat, because it assumes the buyer with the next-highest willingness to pay will pay his or her reservation price, which is generally not realistic. In general, the effect of increasing the number of vouchers up for sale at a given time (the relative change in the selling price with respect to a relative change in the number of vouchers up for sale) will depend on different assumptions about the relative bargaining power of buyers and sellers and the efficiency of exchange.

Table 10-2. Value of a Voucher

| | Ridley and Régnier, 2016 | Robertson, Stefanakis, and Joseph, 2012 |
|--------------------------------------|---|---|
| Dataset and sample of drugs analyzed | <ul style="list-style-type: none"> ▪ The National Prescription Audit and promotional spending data from SDI Health and drugs approved by the FDA from 1/1/2007 to 12/31/2009 | <ul style="list-style-type: none"> ▪ BIO Ventures for Global Health survey and companies with active drug or vaccine programs in one of the 16 PRV-eligible diseases |
| Elements of value considered | <ul style="list-style-type: none"> ▪ Competitive effect (market share) ▪ Time value effect (acceleration of sales) ▪ Exclusivity effect (patent) | <ul style="list-style-type: none"> ▪ Estimated reasonable investment to receive a PRV ▪ Expected return for the sale of a PRV |

(continued)

Table 10-2. Value of a Voucher (continued)

| | Ridley and Régnier, 2016 | Robertson, Stefanakis, and Joseph, 2012 |
|--|---|--|
| Average value or price of voucher in the baseline scenario | <ul style="list-style-type: none"> ▪ \$234 million value—in 2014 dollars ▪ 95% confidence interval from Monte Carlo simulations: (\$45 million to \$657) | <ul style="list-style-type: none"> ▪ \$179.6 million price—in 2011 dollars ▪ + 1 Service Delivery: (\$56.2 million to \$303 million) |
| Dilution effect | <ul style="list-style-type: none"> ▪ Value of voucher falls by 50% as the number of vouchers increases by 300% ▪ Implied elasticity of value voucher of -.167 | <ul style="list-style-type: none"> ▪ Not considered |
| Sensitivity analyses | <ul style="list-style-type: none"> ▪ Acceleration approval, the number of vouchers issued per year, sales projections, and order of market entry | <ul style="list-style-type: none"> ▪ Size of company |

Source: Ridley & Régnier (2016); Robertson, Stefanakis, and Joseph (2012); Kesselheim et al. (2015); Silverman (2015)

To see the effect of bargaining power, first assume the seller has all the bargaining power. If there is only one voucher up for sale, the seller will extract a price of \$234 million (the reservation price of the buyer with the highest willingness to pay). If there are five vouchers up for sale, each seller will receive the reservation price of the buyer with either the first-, second-, third-, fourth-, or fifth-highest willingness to pay, so he would expect to receive a price of \$116 million (averaging \$234, \$130, \$104, \$76, and \$38 million), which is 50% of \$234 million.

Now suppose the seller has somewhat less bargaining power and can expect to receive the reservation price of the buyer with the next-highest willingness to pay (the alternative buyer), then if there is only one voucher to sell, that seller would expect to receive \$130 million. If there are five vouchers up for sale, each seller will receive the reservation price of the buyer with either the second-, third-, fourth-, fifth-, or sixth-highest willingness to pay, so the seller would expect to receive a price of \$75 million (averaging \$130, \$104, \$76, \$38, and \$26 million), which is 58% of \$130 million.

If we assume that buyers have much more bargaining power and that all vouchers sell for the same price, namely the reservation price of the (n+1)th buyer when there are n vouchers to sell, then the price with a single voucher up for sale is \$130 million, and the price with five vouchers up for sale is \$26 million, which is 20% of \$130 million.

These results suggest that the dilution effect is quantitatively sensitive to assumptions about bargaining power, but the qualitative point that the dilution effect is likely to be substantial is rather robust.

With five vouchers in circulation at the time of this analysis, which was conducted in Spring 2016, (two having been sold once by the original awardee and three still held by the original awardee), the dilution effect illustrated in Figure 10-2 is of practical importance. A voucher worth \$100 to \$200 million (as in Figure 10-2 with one or two vouchers in circulation) arguably provides an incentive that would be difficult for a government agency or agencies to match by other means. If the voucher is worth only \$30 million (as in Figure 10-2 with five or more vouchers in circulation), the incentive effect is much smaller. Thus, the inability to control the number of vouchers awarded over a span of time may lead pharmaceutical companies to discount the expected value of the voucher and perceive a much smaller incentive effect of PRVs.

10.3 Sensitivity of Incentive Effect to Development Cost

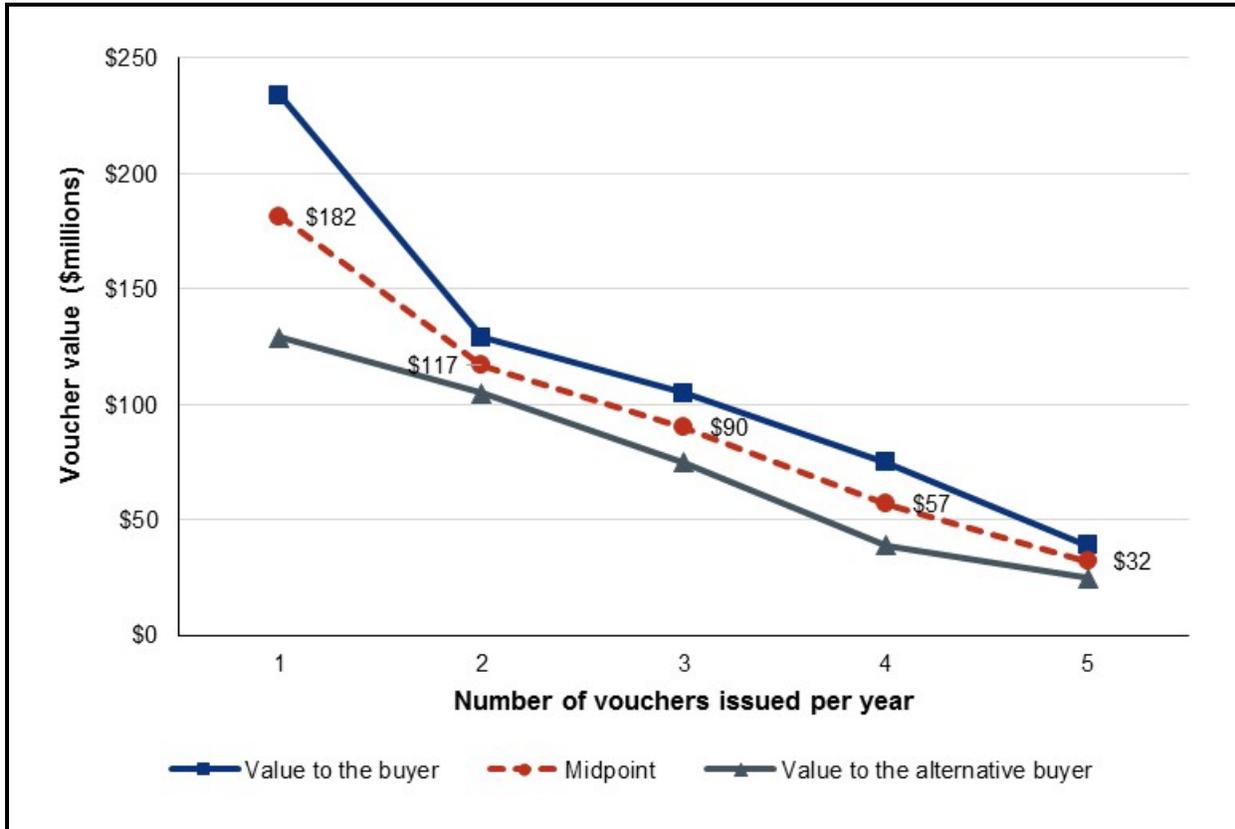
This section introduces a quantitative model of the expected net present value of drug candidates in development and uses this model to characterize situations in which a PRV program would or would not alter incentives.

Following the approach in Scott et al. (2014), we calculated the expected cost of developing a new drug by summing the risk-adjusted capitalized costs of each phase of development:

$$Expected\ Cost = \left(c \int_{t_{end}}^{t_{start}} e^{rt/12} dt \right) / p = \left(\frac{c}{p} \right) \left(\frac{12}{r} \right) (e^{rt_{start}/12} - e^{rt_{end}/12}). \quad Eq. 1$$

In this formula, c is the cost per month, per compound in each phase; p is the probability that a compound in this phase is ultimately approved for marketing; r is the cost of capital as an annual rate; and t_{start} and t_{end} are the time in months from the start and end of the phase, respectively, to the date of drug approval.

Figure 10-2. Voucher Value by Number of Vouchers



Note: Adapted from Ridley and Régnier (2016). Added the dotted orange line, which represents the estimated values to the buyer and alternative buyer.

As r approaches zero, out-of-pocket costs can be recovered from this formula. When r takes on an appropriate value for a pharmaceutical company’s cost of capital, the formula adds up the accumulated costs of each stage of drug development together with the amount of interest that would accrue, at the annual rate r , from the moment the cost is incurred until the expected date of drug approval (launch). In addition, each stage’s costs are divided by the probability, p , that a compound in that phase is ultimately approved. Since the cost, c , measures the rate at which costs accumulate per month per drug candidate in development, dividing by the probability p is equivalent to multiplying by the number of candidates that must enter that stage of development for every expected launch.

Table 10-3 summarizes the baseline parameter values used for the modeling. We assume a cost of capital of 10.5% per year, as an annually compounded rate, which is equivalent to a continuously compounded rate of 10.0%, which gives us the value r in the formula for expected cost. The transition probabilities are multiplied to give the conditional probability of approval, conditional on a drug candidate’s entering a given phase. Finally, the value c for each phase for the expected cost formula can be obtained by dividing the out-of-pocket costs for each phase by its respective duration, given in Table 10-3. We can then calculate

the expected cost for each phase, using the formula with the appropriate parameter values, as summarized in Table 10-4.

Table 10-3. Baseline Parameter Values

| Phase | Transition Probabilities | Start to Start Months |
|---|--------------------------|-----------------------|
| Preclinical (Synthesis to Phase 1) | 1 (by construction) | 31.2 |
| Phase 1 to 2 | 0.868 | 19.8 |
| Phase 2 to 3 | 0.700 | 30.3 |
| Phase 3 to NDA/BLA submission | 0.670 | 30.7 |
| NDA/BLA submission to approval | 0.810 | 16.0 |

| Phase | Duration, Months | Out-of-Pocket Costs, \$ Millions per Molecule in Development |
|-------------|------------------|--|
| Preclinical | 31.2 | 50.9 |
| Phase 1 | 33.1 | 17.3 |
| Phase 2 | 37.9 | 44.8 |
| Phase 3 | 45.1 | 200.0 |
| Review | 16.0 | 0.00 |

Notes: Clinical phases overlap, as can be seen by comparing Start to Start Months in the upper part of the table with Duration, Months in the lower part. For example, Phase 2 begins on average 19.8 months after the beginning of Phase 1, but the average duration of Phase 1 is 33.1 months, implying an overlap of 13.3 months. Transition probabilities are for drug candidates with orphan drug designation from Hay et al. (2014). All other parameters are from DiMasi, Grabowski, and Hansen (2016); out-of-pocket costs are median values.

Table 10-4. Baseline Parameter Values

| Phase | p | c | t _{start} | t _{end} | \$ millions | |
|-------------|-------|--------|--------------------|------------------|---------------|----------------|
| | | | | | Expected Cost | Private Hurdle |
| Preclinical | 0.330 | 1.6314 | 128.0 | 96.8 | 394 | 1,142 |
| Phase 1 | 0.330 | 0.5227 | 96.8 | 63.7 | 103 | 748 |
| Phase 2 | 0.380 | 1.1821 | 77.0 | 39.1 | 192 | 645 |
| Phase 3 | 0.543 | 4.4346 | 46.7 | 1.6 | 453 | 453 |
| Review | 0.810 | 0 | 16.0 | 0 | 0 | 0 |

Note: The private hurdle for a given phase is the sum of the expected cost of that and all subsequent phases; it is the minimum return, valued at the date of launch, a company must expect for it to prefer to go forward with development (equivalently, for it to perceive a positive expected net present value of developing the drug).

Having calculated the expected cost for each phase, we can then calculate the private hurdle for each phase as the sum of the expected cost of that and all subsequent phases. The private hurdle is the minimum return, valued at the date of launch, a company must expect for it to prefer to go forward with development. Equivalently, it is the minimum

return for which a company perceives a positive expected net present value of developing the drug. The private hurdle for entering any phase does not include the expected cost of any prior phase. Thus, the private hurdle for Phase 1 does not include the expected cost of preclinical development, which is a sunk cost at the beginning of Phase 1.

Using the baseline parameter values, the private hurdles for a pharmaceutical company to move forward with drug development are \$1,142 million at the beginning of preclinical development and \$748 million, \$645, and \$453 million at the beginning of Phases 1, 2, and 3, respectively. Therefore, the company is willing to begin preclinical development if the private value of developing the drug is at least \$1,142 million. Likewise, the company is willing to enter first-in-human trials if the private value is at least \$748 million, and so on.

In a world where vouchers exist, if the expected market for the drug is at least \$1,142 million, the drug would be developed with or without the voucher. If the private value is less than \$1,142 million but greater than \$1,142 million minus the expected value of the voucher, then the voucher has the effect of making the pharmaceutical company willing to invest in preclinical development of the drug.

For example, if a pharmaceutical company develops a drug and estimates its value at \$200 million, we assume the company is certain that the voucher will be available in 9 years when it submits its NDA or BLA. From Table 10-3, the average time from the start of preclinical studies to NDA or BLA submission is 9 years and 4 months. For simplicity, we also assume the \$200 million value is realized by the company on the date the drug is approved (which is realistic if the company has lined up a buyer for the voucher ahead of time). Under these assumptions, if the company expects the private value of the drug to be less than \$942 million, developing the drug is not worthwhile even with the voucher. If the company expects the private value to be between \$942 million and \$1,142 million, the voucher will incentivize the company to develop the drug. This example is easily generalized to any expected voucher value. In the example, we focused on the private hurdle minus \$200 million, but this is equal to the private hurdle minus the expected value of the voucher.

Continuing with this example, suppose the private value of the drug is \$1,100 million and the social value is \$1,200 million. In this situation, the voucher raises the private value of developing the drug to \$1,300 million, which is \$100 million more than the drug is worth to society. This is not necessarily a big problem, especially if the social cost of providing the voucher is much lower than its \$200 million value to the pharmaceutical company. Still, it is worth thinking about this example and recognizing that an ideal policy intervention might seek to provide the relatively small incremental incentive needed (only \$42 million in this case) by some other means and use a PRV when the social spillover is much larger or the incremental incentive needed is much larger.

As development proceeds through successive phases, more costs are sunk, and the private hurdle to continue development typically falls.¹⁷ This can be seen in Table 10-4 and illustrated with our example, keeping the voucher value fixed at \$200 million. The voucher would have an effect on this company at the beginning of Phase 1 if private value was expected to be between \$548 million and \$748 million, at the beginning of Phase 2 if private value was expected to be between \$445 and \$645 million, and at the beginning of Phase 3 if private value was expected to be between \$253 and \$453 million. If private value is above these ranges, the voucher has no incentive effect because the drug would have been developed anyway—the private value being greater than the private hurdle even without the voucher.

We can also generalize this example to any parameter values, different from the baseline values given in Tables 10-3 and 10-4. The following figures illustrate the sensitivity of private hurdles to changes in these parameter values. In each figure, one parameter is varied while all others are held fixed at their baseline values. In each figure, a horizontal dashed line indicates the baseline private hurdles from Table 10-4.

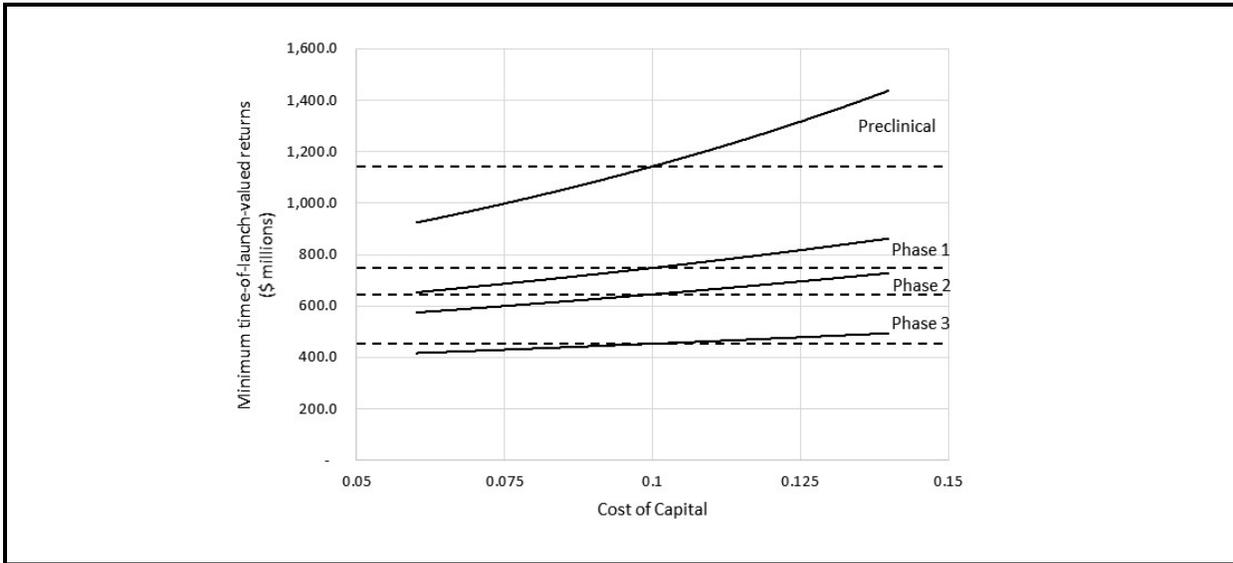
Figure 10-3 shows the effect of varying capital costs from 6% to 14%, a range slightly wider than that identified by Harrington (2012). Capital costs matter more for earlier stages of development, indicated by steeper curves, because they are applied over a greater length of time between investment outlays and expected date of drug approval. Private hurdles range from \$924 to \$1,439 million for preclinical, \$653 to \$863 million for Phase 1, \$575 to \$728 million for Phase 2, and \$417 to \$494 million for Phase 3.

Figure 10-4 shows the effect of varying the probability of drug approval, conditional on having made it to Phase 2. In this analysis, we allow the probability of entering Phase 3, conditional on making it to Phase 2, to vary. The probability of approval, conditional on making it to Phase 3, is held constant at 0.54 (which is 0.67×0.81).¹⁸ For drug candidates that receive orphan drug designation, Hay et al. (2014) reports a Phase 2 to 3 transition probability of 0.70, corresponding to a Phase 2 to launch probability of 0.38 in Figure 10-4 (labeled with the vertical line “Hay, Orphan”). For all drug candidates, Hay et al. (2014) report a Phase 2 to 3 transition probability of 0.32, corresponding to a Phase 2 to launch probability of 0.18 (labeled with the vertical line “Hay, All”). DiMasi, Grabowski, and Hansen (2016) report a similar Phase 2 to 3 transition probability of 0.36 and the current range also captures transition probabilities reported by Bio (2016).

¹⁷ There are certainly exceptions. For example, information gleaned from a Phase 2 trial could suggest that a Phase 3 trial needs to be longer than expected and enroll additional patients, causing the private hurdle for Phase 3 to be higher than the hurdle that had been perceived for Phase 2.

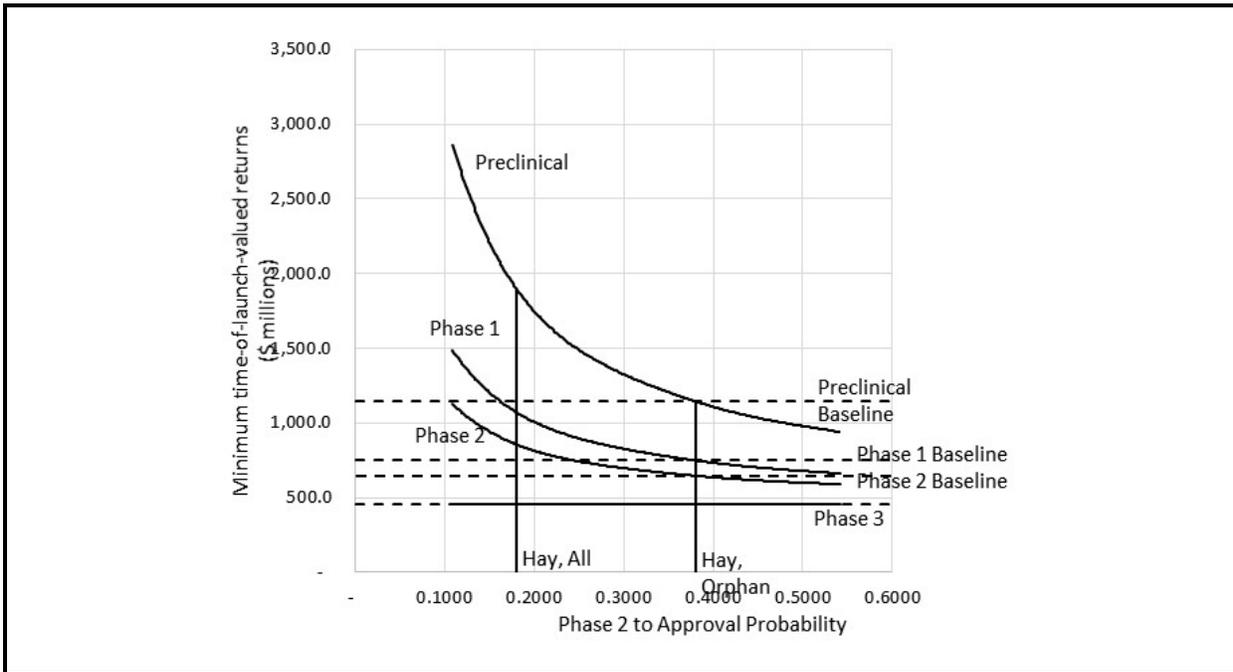
¹⁸ Note that the private hurdle for Phase 3 is therefore constant (at its baseline value of \$453 million) because the expected return required for going forward with Phase 3 does not depend on the probability of getting to Phase 3.

Figure 10-3. Effect of Varying Capital Cost and Phase 3 Cost on Private Hurdles



Note: Parameters other than the cost of capital are held constant at their values in Figure 10-4. Dashed lines indicate the baseline private hurdles.

Figure 10-4. Effect of Varying Phase 2 to Approval Probability on Private Hurdles

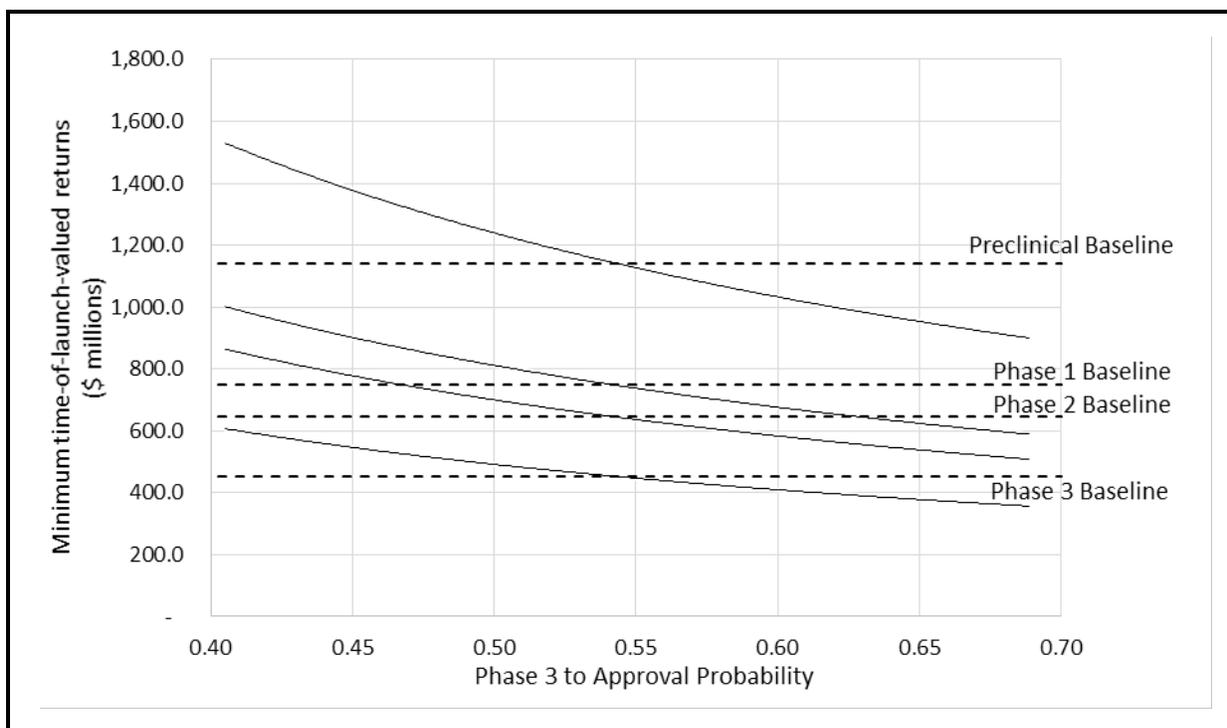


Note: Parameters other than Phase 2 to 3 transition probabilities are held constant at their values in Figure 10-4. Dashed lines indicate the baseline private hurdles.

Figure 10-5 shows the effect of the probability of approval, conditional on entering Phase 3. This probability is varied in the figure by varying only the probability of reaching NDA or BLA submission, conditional on entering Phase 3. The probability of approval, conditional on NDA

or BLA submission, is held constant at 0.81. Estimates of Phase 3 to launch probabilities are less wide ranging than Phase 2 to launch probabilities. Hay et al. (2014) report a Phase 3 to launch probability of 0.50 (based on Phase 3 to NDA probability of 0.60 and NDA launch of 0.83) for all drugs and 0.54 for orphan drugs (based on a 0.67 Phase 3 to NDA transition probability and 0.81 NDA to launch transition probability). DiMasi, Grabowski, and Hansen (2016) report a similar Phase 3 to launch probability of 0.56 (based on 0.62 Phase 3 to NDA and 0.90 NDA to launch).

Figure 10-5. Effect of Varying Phase 3 to Approval Probability on Private Hurdles

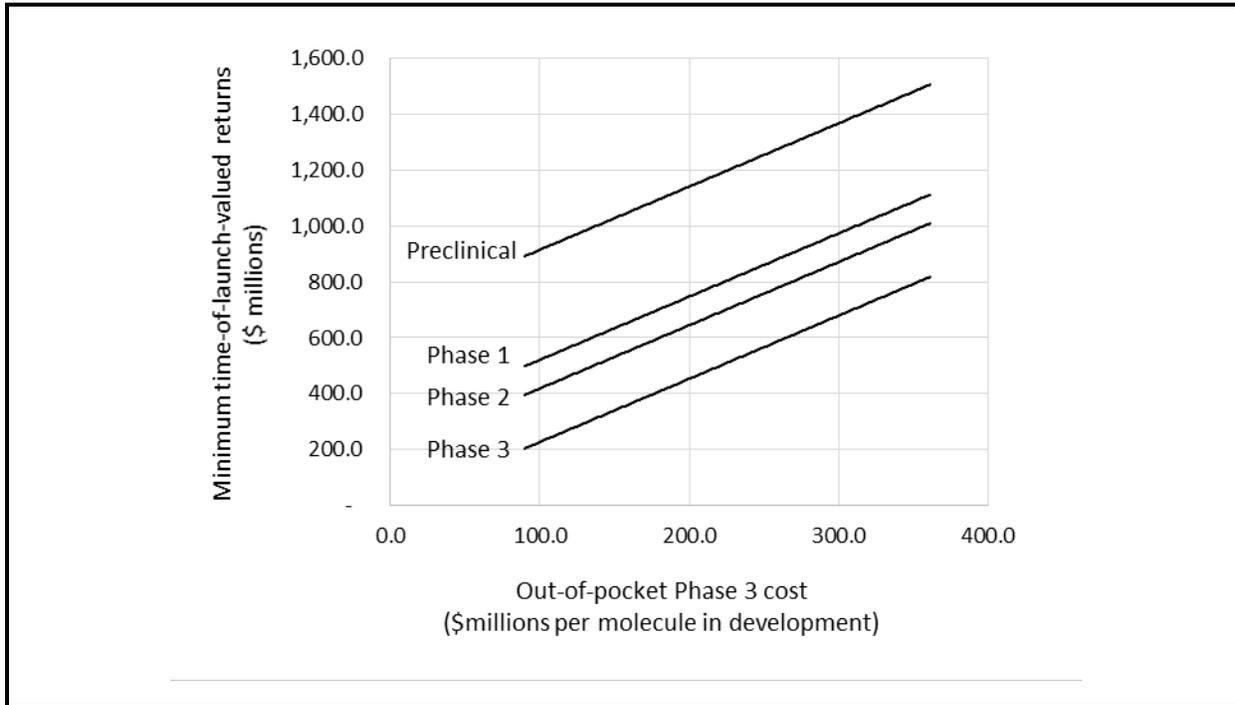


Note: Other parameters are held constant at their values in Figure 10-5. Dashed lines indicate the baseline private hurdles.

Figure 10-6 shows the effect of the out-of-pocket costs of Phase 3. DiMasi, Grabowski, and Hansen (2016) report a median cost of \$200 million and average cost of \$255 million with a \$153 million standard deviation, suggesting that this cost can vary widely. Even for a wide range of costs, required present value returns for clinical stages are between \$200 million and \$1.1 billion.

Our analysis suggests that a drug candidate that has made its way at least into Phase 1 is unlikely to need the added incentive of a voucher to spur continued development if the private value of marketing the drug is expected to be much more than \$1 billion. Under most if not all parameter value assumptions, the private hurdle for Phase 1 was around \$1 billion or less where the voucher has no incentive effect.

Figure 10-6. Effect of Phase 3 Cost on Private Hurdles



Note: Other parameters are held constant at their values in Figure 10-4. Dashed lines indicate the baseline private hurdles.

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11. SUMMARY AND CONCLUSIONS

R&D investment for new drug products is concentrated in the development of drugs with high expected revenues or significant profits, leaving many medical needs, such as those that affect a small number of patients, unaddressed. In this report, we reviewed seven policy tools that have the potential to increase R&D for drugs that address unmet medical needs. The policy tools vary in their mechanisms for increasing investment in drug development. They also vary in their ability to target specific stages of development, therapeutic areas, and innovator characteristics. Table 11-1 summarizes the key features of each policy tool.

Accelerators are useful for encouraging and supporting preclinical development. Their combination of funding and services is oriented toward increasing the probability that a promising discovery does not falter for want of support, overcoming at least some of the funding and knowledge gaps innovators face, and de-risking the technology in the eyes of potential investors. Accelerators' impact is on identifying and maturing promising technologies that otherwise could go unsupported. Given this focus, they are most useful for academic innovators and small pharmaceutical companies. With a lens toward unmet medical needs, accelerators can be targeted to specific therapeutic areas and technologies. If an accelerator has a pipeline from which to draw and the state of the science is sufficient, it could cultivate a portfolio of early-stage technologies for follow-on investment, although the costliest development stages are those beyond an accelerator's typical scope.

R&D tax credits may be another useful tool for encouraging early-stage R&D, especially if they incorporate a refundable design, which allows pharmaceutical companies to recoup a portion of their R&D spending, even if it exceeds tax liability. Both accelerators and R&D tax credits have the potential to increase investment in drug candidates by lowering the private hurdle rate. A drawback of tax credits is that they can be difficult to target, and they lack the selectivity that accelerators feature. The combination of an accelerator project and tax credits may permit smaller pharmaceutical companies to take on more ambitious development projects, both in terms of risk and in terms of cost.

Patent and regulatory exclusivity extensions have the potential to raise revenues by providing a pharmaceutical company with a longer time after FDA approval to market a drug free from generic competition. Extensions and other policy tools that increase drug revenues after approval are most likely to incentivize later stages of development, where the early-stage risk has been eliminated. Without sufficient demand for a drug, extensions alone are unlikely to raise private revenue enough to offset development costs.

For this reason, various delinkage approaches, which provide a reward for drug development that is completely or partially separate from product revenues, may be promising tools. Delinkage approaches encourage drug development by increasing expected

revenues, ideally raising revenues just enough to move the drug project to above the private hurdle rate. Prizes are an example of partial delinkage, whereby the drug developer obtains a monetary prize if certain criteria for drug development are met. In the case of prizes, the pharmaceutical company typically also retains any profits from sales of its drug, thus, not fully delinking the reward from drug sales. Delinkage approaches may also be designed to reward early-stage milestones, which would serve to reduce development costs in addition to raising revenues when a later stage or drug approval is achieved. Like accelerators, delinkage approaches can be targeted by therapeutic area, technology, and stage of development.

Prizes require a commitment from funders (e.g., U.S. government) to pay a given amount when drug development criteria are met. Other partial delinkage approaches, such as PRVs and wildcard exclusivity vouchers, instead rely on the robust market for higher-profit drug products to provide a reward that is sufficient to incentivize new projects. PRVs, by allowing pharmaceutical companies to obtain a priority review for a high-profit drug or to sell the voucher, currently provide rewards that have been valued by pharmaceutical companies at between \$68 million and \$350 million, rewards that may be large enough to push a number of potential drug projects into a profitable range. However, the value of PRVs is uncertain, and the value of each awarded and unused voucher is likely to decline as more PRVs are awarded. An important challenge for PRV program design, therefore, is to effectively target high-priority unmet drug needs and not expand PRV programs so broadly that PRV values decline to a point where they have little incentive effect.

Wildcard exclusivity vouchers have not been used in the United States. However, because they can be used to extend marketing exclusivity for high-profit drugs, the value of exclusivity vouchers may be much larger than that of PRVs, given that the top-selling drugs in the United States have annual sales of \$5 billion or more. Yet, targeting for exclusivity vouchers is especially important to help ensure that only those drug products that truly need very large incentives for R&D receive these awards. Otherwise, most of the benefits could accrue to pharmaceutical companies at the expense of patients and payers. Drugs that can best be incentivized by exclusivity vouchers may include those expected to have high development costs, long timelines, significant risks, and/or a small market.

Finally, AMCs are a type of delinkage that partially or fully decouples the drug development reward from sales by providing a commitment prior to a drug's being developed to buy a given product volume at a given price for a given amount of time. AMCs reduce market uncertainty. However, because of the scientific risks at the time of early-stage investment in a drug candidate (e.g., whether another company will meet the criteria for reward first), AMCs probably need to be combined with other policy tools to be successful. The guaranteed revenue aspect of AMCs may be incorporated into other policy approaches, such as patent and regulatory exclusivity extension policies, to improve their targeting and increase their effectiveness.

When considering a strategy to obtain drug development that targets a specific area of unmet need, combinations of several of the seven policy tools may result in a comprehensive approach for achieving these drug development goals. For example, both accelerators and R&D tax credits may be needed to encourage early-stage development and help reduce the private hurdle rate faced by pharmaceutical companies. These policies could work together to reduce private costs considerably, thus reducing the risk of early-stage investment.

To incentivize later stages of development, including costly clinical trials, incentives that aim to raise revenues for approved drug products may be needed. Although combinations of these incentives could be used, the policies may be most effectively targeted by carefully considering how much additional revenue is needed to encourage drug development for a specific need. A drug candidate with particularly high costs, a long development time, and a small potential market could likely benefit from an especially large incentive, such as that provided by exclusivity vouchers or from a guaranteed revenue incentive, such as the revenue guarantees offered through AMCs.

Drug candidates with lower costs of development or larger potential markets may be incentivized effectively through a longer patent or exclusivity period. PRVs may also be useful for incentivizing drug development because they provide a one-time award that is likely to have a monetary value in the tens or hundreds of millions of dollars. They likely have a value that is greater than that of patent or regulatory exclusivity extensions but lower than the value of an exclusivity voucher. But when considering whether to expand PRV programs, it is important to carefully consider the tradeoffs, as the value of outstanding PRVs may be diluted when additional PRVs are awarded.

All seven of these policy tools face the practical challenge of how to incentivize investments in new drug development that would not otherwise have been undertaken and, in particular, how to avoid rewarding development that would have occurred anyway. Accelerator selection committees are challenged with identifying early-stage R&D projects that they can help move from non-viable to viable candidates for private investment. Choosing the most technically and commercially promising technologies reduces the real impact of the accelerator, because those technologies are more likely to have attracted private investment in the absence of accelerator support. R&D tax credit policy is challenged to remedy private underinvestment in early-stage research and not simply reward companies performing already-profitable commercial development activities. Administrators of innovation prizes—whether the prize takes the form of extended marketing exclusivity, a transferrable voucher for priority review or marketing exclusivity, or a guaranteed minimum sales revenue—are challenged to articulate criteria for awarding the prize so that only the desired innovative activity is encouraged and ultimately rewarded.

This cross-cutting challenge results in unavoidable tradeoffs. Inevitably, accelerators will fund some innovators who would have found willing private investors, R&D tax credits will increase the rate of return on inframarginal investments (those which would have been made anyway) and marginal ones (those that are induced by the policy), and prizes will sometimes be rewarded to companies that did not need an additional incentive to encourage the rewarded R&D investment. One measure of a successful policy is certainly how well it focuses incentives and limits the rewards for drugs that pharmaceutical companies were likely to develop in the absence of policy incentives.

Any given design of each of these policies might be effectively targeted in this way. For example, policies may limit the reward to narrowly defined needs to ensure that those needs are met without rewarding drug development for other needs. Of course, monitoring such criteria is challenging, and because pharmaceutical companies seek to maximize ENPV, they may nonetheless identify ways to qualify for the rewards for drug indications for which they likely would have sought approval anyway. It is challenging to design well-targeted policies, and none of the policy tools described in this report can easily overcome this challenge.

However, the magnitude and incidence of the anticipated cost when mistargeting occurs differs considerably across the seven policy tools. Part of the cost of a mistargeted priority review voucher, for instance, is to dilute the value of other vouchers; a voucher policy in which the award criteria are overly broad therefore offers weaker incentives, because drug developers anticipate a larger supply of vouchers relative to the number of high-ENPV drugs nearing FDA review at any given time and therefore expect lower values for available PRVs than recently sold PRVs. Similarly, the launch of a new voucher program, especially a poorly targeted one, can undermine the incentive effect of a separate, well-targeted one because of this anticipated dilution effect.

The social cost of a PRV when it is redeemed falls on an uncertain mix of patients and payers, depending on how FDA chooses to reallocate resources to provide the priority review required by the voucher (i.e., potentially drawing staff from other public health priorities). If wildcard exclusivity vouchers were to become part of the policy landscape, the value of exclusivity vouchers to awardees would come at the expense of patients treated with and associated payers of unrelated drugs for which the vouchers are used.

Policies that place the cost of incentivizing one area of drug development on unrelated stakeholder groups will always raise questions of equity and fair treatment. In contrast, policies that spread the cost burden more widely are less likely to raise such concerns. For example, R&D tax credits spread the burden over the entire tax base, so they result in a small cost to each taxpayer.

In sum, an optimal policy approach to increase drug development for needed new drugs in a socially beneficial manner might combine elements of multiple policy tools to both reduce

private costs and raise private revenues, while incentivizing only needed new drug development and not rewarding drug development that would have occurred in the absence of the policy. An additional consideration is how to achieve the drug development goals without imposing large costs on patients, payers, and other stakeholders.

An important knowledge gap is the lack of analyses on or, where analyses have been conducted, lack of consensus around the expected social benefits of each policy tool. Additional efforts to standardize approaches for valuing the impact of potential new drugs could help improve value assessments and the allocation of drug development resources.

Additional research is also needed on the combined impacts of the policy tools to better understand whether using tools together, such as R&D tax credits and exclusivity extensions in the Orphan Drug Act, yields more of the desired drug development than simply implementing one or the other policy. It will also be useful to assess whether some policies should be viewed as substitutes, while others may be viewed as complements.

Table 11-1. Comparison of the Seven Policy Tools

| Policy Rationale: Barriers Addressed and Intended Impacts | Ability to Target Socially Beneficial R&D that Would Not Otherwise Have Been Undertaken | Appropriate Conditions for Use of PT | Limitations and Disadvantages | Examples and Selected Summary Statistics |
|---|--|---|---|---|
| Accelerators | | | | |
| <ul style="list-style-type: none"> ▪ Provide funding for early-stage validation and proof-of-concept studies to allow products to progress to later stages of development. ▪ Reduce R&D cost, time, and risk. No impact on expected revenue. | <p>Design.</p> <ul style="list-style-type: none"> ▪ Awards can be highly targeted and value set at policymakers' discretion. ▪ Is limited only by the specific expertise of the selection committee. <p>Evidence.</p> <ul style="list-style-type: none"> ▪ Overall effectiveness currently unclear; preliminary data and results are promising. | <p>Therapeutic areas.</p> <ul style="list-style-type: none"> ▪ Areas where basic research is underdeveloped. <p>Stages of development.</p> <ul style="list-style-type: none"> ▪ Most valuable in early stages of development when product validation is most critical. <p>Company size.</p> <ul style="list-style-type: none"> ▪ Encourages participation predominantly among small firms. | <p>Separating problem.</p> <ul style="list-style-type: none"> ▪ Challenging to identify products that need support and those that do not. ▪ Early-stage funding does not guarantee successful drug development. <p>Social costs.</p> <ul style="list-style-type: none"> ▪ Opportunity costs of dedicated funds on unsuccessful products. ▪ Crowding out of private funding. | <ul style="list-style-type: none"> ▪ Coulter Foundation Translational Partnerships Program. ▪ The NIH Centers for Accelerated Innovation program. ▪ The von Liebig Center for Entrepreneurism. ▪ CARB-X. |
| R&D Tax Credits | | | | |
| <ul style="list-style-type: none"> ▪ Reduce private R&D costs by shifting burden onto the tax base. ▪ Do not affect R&D time or expected revenue after approval. ▪ Could potentially lower risk and the rate of return investors demand. | <p>Design.</p> <ul style="list-style-type: none"> ▪ Incremental vs. volume-based schemes. ▪ Refundable vs. non-refundable. <p>Evidence.</p> <ul style="list-style-type: none"> ▪ Mixed evidence about welfare effects based on international studies. Results highly sensitive to methodological decisions and key assumptions. | <p>Therapeutic areas.</p> <p>Appropriate therapeutic areas are those:</p> <ul style="list-style-type: none"> ▪ With modest expected revenues. ▪ Where the social rate of return to R&D is greater than the private rate of return to R&D. <p>Stages of development.</p> <ul style="list-style-type: none"> ▪ Valuable at all stages, but credit value is highest in the later stages of development because tax credit is proportional to costs. | <ul style="list-style-type: none"> ▪ Administrative costs can be significant for some incremental tax credit programs. ▪ Potential to crowd out private investment in some situations. ▪ Effective tax credit is often lower than the statutory credit because of interactions with other tax laws. | <ul style="list-style-type: none"> ▪ The ODA tax credit and the R&D tax credit offer average annual present value of private R&D cost savings of \$138.8 million for established pharmaceutical companies (Ernst & Young, 2015). ▪ The ODA tax credit alone leads to an estimated \$122.1 million in private annual R&D cost savings. |

(continued)

Table 11-1. Comparison of the Policy Tools (continued)

| Policy Rationale: Barriers Addressed and Intended Impacts | Ability to Target Socially Beneficial R&D that Would Not Otherwise Have Been Undertaken | Appropriate Conditions for Use of PT | Limitations and Disadvantages | Examples and Selected Summary Statistics |
|--|---|--|--|--|
| R&D Tax Credits (continued) | | | | |
| | | <p>Company size.</p> <ul style="list-style-type: none"> Favors established companies with a sufficient tax liability to offset with the credit unless designed to be refundable. | | |
| Patent and Regulatory Exclusivity Extensions | | | | |
| <ul style="list-style-type: none"> Provide additional returns to R&D for qualifying products that have low expected returns. Do not affect R&D cost, time, or risk. | <p>Design.</p> <ul style="list-style-type: none"> Reward is given only for products that meet criteria for FDA approval or other criteria. <p>Evidence.</p> <ul style="list-style-type: none"> U.S. programs have resulted in approvals of many orphan drugs and additional testing in pediatric populations that likely would not have occurred otherwise. | <p>Therapeutic areas.</p> <ul style="list-style-type: none"> Appropriate therapeutic areas are those with sufficient demand to provide increased revenues during extension period. <p>Stages of development.</p> <ul style="list-style-type: none"> Valuable primarily in the later stages of development. Risk and discounting limit value of future reward in early-stage R&D. <p>Company size.</p> <ul style="list-style-type: none"> Encourages participation among both small and large firms. | <p>Social costs.</p> <ul style="list-style-type: none"> Higher prices, resulting from an extended period of limited competition. Reward is largest for most profitable products, although they do not always have the greatest social value. | <ul style="list-style-type: none"> 7-year marketing exclusivity for approved orphan drugs. 6-month data exclusivity for clinical testing in children. |
| Delinkage | | | | |
| <ul style="list-style-type: none"> Provide incentives to invest in R&D independent of volume-based sales revenues for resulting product. Raise expected revenues; do not affect R&D cost, time, or risk. | <p>Design.</p> <ul style="list-style-type: none"> Rewards can be highly targeted to incentivize desired drugs. <p>Evidence.</p> <ul style="list-style-type: none"> Evidence of the effectiveness of innovation inducement prizes is anecdotal and mixed. | <p>Therapeutic areas.</p> <p>Appropriate therapeutic areas are those:</p> <ul style="list-style-type: none"> with limited revenue potential, mainly due to small patient populations, or that address health-related risks that markets do not adequately internalize. | <ul style="list-style-type: none"> Complete delinkage mechanisms (fully decoupling revenues from volume-based sales) are complex to design and implement. Complete delinkage requires credible commitment on part of funders to make reward when criteria are met. | <ul style="list-style-type: none"> DRIVE-AB has proposed and is pursuing two delinkage models—insurance licenses and market entry rewards—among a shortlist of incentives for antibiotic R&D. |

(continued)

Table 11-1. Comparison of the Policy Tools (continued)

| Policy Rationale: Barriers Addressed and Intended Impacts | Ability to Target Socially Beneficial R&D that Would Not Otherwise Have Been Undertaken | Appropriate Conditions for Use of PT | Limitations and Disadvantages | Examples and Selected Summary Statistics |
|--|--|--|---|---|
| Delinkage (continued) | | | | |
| | | <p>Stages of development.</p> <ul style="list-style-type: none"> ▪ May be designed to provide rewards for early-stage milestone achievement and rewards for later stage milestones and approval. <p>Company size.</p> <ul style="list-style-type: none"> ▪ Companies of any size may respond to delinkage incentives. | | |
| Priority Review Vouchers | | | | |
| <ul style="list-style-type: none"> ▪ Provide a financial incentive to invest in R&D for qualifying products that have low expected returns. ▪ Do not affect R&D cost, time, or risk. | <p>Design.</p> <ul style="list-style-type: none"> ▪ Awards limited to products that treat specific indications or qualify for special FDA approval pathways. <p>Evidence.</p> <ul style="list-style-type: none"> ▪ U.S. PRV programs have had limited success in targeting R&D that would not otherwise have occurred. | <p>Therapeutic areas.</p> <p>Appropriate therapeutic areas are those:</p> <ul style="list-style-type: none"> ▪ with limited revenue potential, mainly due to small patient populations, or ▪ that address health-related risks that markets do not adequately internalize. <p>Stages of development.</p> <ul style="list-style-type: none"> ▪ Most valuable in the last stage of development. ▪ Risk and discounting limit voucher value in early-stage R&D. ▪ Anecdotal information suggests that PRVs have motivated early-stage development for some companies. <p>Company size.</p> <ul style="list-style-type: none"> ▪ Encourages participation among both small and large firms. | <p>Dilution effect.</p> <ul style="list-style-type: none"> ▪ Expected value of PRVs is reduced as more vouchers are awarded. <p>Social costs.</p> <ul style="list-style-type: none"> ▪ Increased burden on FDA review process not fully offset by fees. ▪ Priority reviews triggered by a PRV may divert FDA resources away from drugs with potentially greater public health impact. ▪ Value of the voucher is not adjustable by policymakers. ▪ Value of the voucher is uncertain. ▪ Value is unknown at the time of R&D decisions. | <ul style="list-style-type: none"> ▪ U.S. PRV programs for rare pediatric disease, neglected tropical disease, and medical countermeasures. ▪ 16 new drugs have been awarded PRVs as of August 31, 2017. ▪ At least 7 vouchers have been sold and 7 have been redeemed as of August 31, 2017. ▪ U.S. PRVs have sold for \$65 million–\$350 million, with the most recent reported purchase for \$130 million. |

(continued)

Table 11-1. Comparison of the Policy Tools (continued)

| Policy Rationale: Barriers Addressed and Intended Impacts | Ability to Target Socially Beneficial R&D that Would Not Otherwise Have Been Undertaken | Appropriate Conditions for Use of PT | Limitations/ Disadvantages | Examples and Selected Summary Statistics |
|---|--|---|---|--|
| Wildcard Exclusivity Vouchers | | | | |
| <ul style="list-style-type: none"> ▪ Could provide a financial incentive to invest in R&D for qualifying products that have low expected returns. ▪ Would not affect R&D cost, time, or risk. | <p>Design.</p> <ul style="list-style-type: none"> ▪ Awards could be limited to drugs that treat specific indications or qualify for special FDA approval pathways. ▪ Would need to be very narrowly targeted to ensure that only desired new drugs are incentivized. | <p>Therapeutic areas. Appropriate therapeutic areas are those:</p> <ul style="list-style-type: none"> ▪ with limited revenue potential, mainly due to small patient populations, or ▪ that address health-related risks that markets do not adequately internalize. <p>Stages of development.</p> <ul style="list-style-type: none"> ▪ Most valuable in late stages of development, but the large potential size of reward could also affect earlier stage decisions. <p>Company size.</p> <ul style="list-style-type: none"> ▪ Encourages participation among both small and large firms. | <p>Social costs.</p> <ul style="list-style-type: none"> ▪ Would delay generic entry in profitable drug markets, benefiting pharmaceutical companies at the expense of patients and payers. | <ul style="list-style-type: none"> ▪ To date, exclusivity vouchers have not been used. |
| Advance Market Commitments (AMCs) | | | | |
| <ul style="list-style-type: none"> ▪ Guarantee a fixed amount of post-production revenue. ▪ Guarantee a market upon approval. ▪ Do not affect R&D cost or time. | <p>Design.</p> <ul style="list-style-type: none"> ▪ Awards can be targeted to address specific indications. <p>Evidence.</p> <ul style="list-style-type: none"> ▪ No AMC programs have been successful domestically. AMCs for vaccines internationally have shown mixed success. | <p>Therapeutic areas. Appropriate therapeutic areas are:</p> <ul style="list-style-type: none"> ▪ Those where purchasers possess market power <p>Stages of development.</p> <ul style="list-style-type: none"> ▪ Effective when targeted at products in later stages of R&D to reduce uncertainty around market size and because of the time value of money. <p>Company size.</p> <ul style="list-style-type: none"> ▪ Policy encourages participation from large firms that have the capacity to produce. | <p>Design challenge.</p> <ul style="list-style-type: none"> ▪ Incorrect forecasting of proper market size, price, and product specifications could result in no product being developed or waste of funds. ▪ AMCs require a large and credible commitment to sustain the market. | <ul style="list-style-type: none"> ▪ Pneumococcal vaccine programs to provide vaccine for developing countries at cost. ▪ 1994 agreement between UK government and vaccine companies resulted in the development of a vaccine for meningitis C. ▪ Proposals for two AMCs for malaria vaccines were never undertaken successfully. |

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Appendix A PRV-Awarded Drugs

This section provides an overview of the 16 drugs that have been awarded PRVs, five for neglected tropical diseases and eleven for rare pediatric diseases. Table A.1 provides a summary.

Table A.1. PRV Awards

| Program | Drug | Sponsor | Drug Summary | Voucher Summary |
|------------------------------------|---|---|---|---|
| Neglected Tropical Diseases | Coartem Tablets (artemether-lumefantrine) | Novartis | Antimalarial developed by researchers at the Institute of Microbiology and Epidemiology in Beijing. When approved by FDA in 2009, Coartem was already approved in more than 80 other countries. Novartis has delivered 750 million treatments since 2001 and has pledged not to enforce its patent. | Novartis redeemed the voucher in 2011 on canakinumab for gouty arthritis (the indication was rejected). |
| | Sirturo (bedaquiline) | Janssen Therapeutics | Approved by FDA in 2012, Sirturo is part of a combination therapy for multi-drug resistant tuberculosis. | Used on Tremfya (guselkumab); approved in July 2017 to treat moderate to severe plaque psoriasis. |
| | Impavido (miltefosine) | Knight Therapeutics | Approved by FDA in March 2014 to treat leishmaniasis; originally developed for cancer, Impavido has been licensed outside the United States for leishmaniasis since 2004. | Sold to Gilead in November 2014 for \$125 million. Redeemed on Odefsey, approved in March 2016 as a complete regimen drug for HIV-1. |
| | VaxChora (CVD 103-HgR) | PaxVax Bermuda | The first cholera vaccine approved in the U.S., VaxChora was previously approved and marketed in six countries under the brand name "Orochol." | Likely sold to Gilead for ~\$200 million |
| | Benznidazole | Chemo Research | The first treatment for Chagas disease in the United States; approved for use in children aged 2 to 12 years. Awarded August 29, 2017. | Not yet sold or redeemed. |
| Rare Pediatric Diseases | Vimizim (elosulfase alfa) | BioMarin Pharmaceutical | Approved by FDA in February 2014, Vimizim is the first FDA-approved treatment for Mucopolysaccharidosis Type IVA (Morquio A syndrome), a rare, autosomal recessive lysosomal storage disease. The pivotal trial for Vimizim was launched 17 months before the rare pediatric PRV program took effect. | Sold to Regeneron and Sanofi in July 2014 for \$67.5 million. Redeemed on the PCSK9-inhibitor alirocumab, approved in July 2015 for the treatment of familial hypercholesterolemia. |
| | Cholbam (cholic acid) | Retrophin (formerly Askleion Pharmaceuticals) | Approved by FDA in March 2015 to treat rare bile acid synthesis disorders. Efficacy and safety of Cholbam had been demonstrated in an investigator-initiated trial begun in 1994. | Sold to Sanofi in July 2015 for \$245 million. Redeemed in December 2015 on LixiLan, a fixed-ratio combination of lixisenatide and insulin glargine for the treatment of type 2 diabetes; approved in November 2016. |
| | Unituxin (dinutuximab) | United Therapeutics | Approved by FDA in March 2015 as part of a first-line therapy for high-risk neuroblastoma, Unituxin was largely developed by NCI, with United Therapeutics being selected at a late stage of development to commercialize the drug. | Sold to AbbVie in August 2015 for \$350 million. Not yet redeemed. |
| | Xuriden (uridine triacetate) | Wellstat Therapeutics | Approved by FDA in September 2015, Xuriden treats an extremely rare eye disorder, hereditary orotic aciduria. FDA approached Wellstat to continue development of the drug when the previous sole supplier discontinued its development program. | Wellstat negotiated a deal in 2014 to transfer the voucher to AstraZeneca upon FDA approval of the drug. Details are undisclosed. Not yet redeemed. |

(continued)

Table A.1. PRV Awards (continued)

| Program | Drug | Sponsor | Drug Summary | Voucher Summary |
|---------|-----------------------------|---|---|---|
| | Strensiq (asfotase alfa) | Alexion Pharmaceuticals | Approved by FDA in October 2015, Strensiq is the first treatment approved for perinatal, infantile, and juvenile-onset hypophosphatasia a rare, genetic, progressive, metabolic disease leading to severe disability and life-threatening complications. | Not yet sold or redeemed. |
| | Kanuma (sebelipase alfa) | Alexion Pharmaceuticals | Approved by FDA in December 2015, Kanuma is the first treatment for lysosomal acid lipase deficiency; patients with the disease rarely survive beyond 1 year. | Not yet sold or redeemed. |
| | Exondys 51 (eteplirsen) | Sarepta Therapeutics | Approved by FDA in September 2016, Exondys 51 is a gene therapy that treats a confirmed mutation of the dystrophin gene that affects about 13% of the population with Duchenne muscular dystrophy (DMD). Patients with DMD suffer from degeneration of skeletal and cardiac muscle resulting in loss of function in childhood and adolescence and premature death from respiratory or cardiac failure in adulthood. | Sold to Gilead Sciences in February 2017 for \$125 million. Gilead used a PRV in June 2017 for an investigational, fixed-dose combination of bicitegravir and emtricitabine/tenofovir alafenamide to treat HIV. Priority review granted by FDA in August 2017. |
| | Spinraza (nusinersen) | Biogen (under a licensing partnership with Ionis Pharmaceuticals) | Approved by FDA in December 2016, Spinraza is indicated for treatment of spinal muscular atrophy (SMA) in children and adults. SMA is a rare and often fatal genetic disease affecting muscle strength and movement. | Not yet sold or redeemed. |
| | Emflaza (deflazacort) | PTC Therapeutics (initially Marathon Pharmaceuticals) | Approved by FDA in February 2017, Emflaza is an anti-inflammatory corticosteroid indicated for treating DMD patients. Prior to the FDA approval, deflazacort was available in Canada, Europe, and the United Kingdom, and had been imported into the United States for decades by some DMD patients. | Not yet sold or redeemed. The PRV is still held by Marathon Pharmaceuticals, although the drug was sold to PTC Therapeutics. |
| | Brineura (cerliponase alfa) | BioMarin Pharmaceutical | Approved by FDA in April 2017, Brineura is an enzyme replacement therapy for late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), an extremely rare and fatal neurodegenerative condition. About 20 children in the United States are born with CLN2 each year. | Not yet sold or redeemed. |
| | Kymriah (tisagenlecleucel) | Novartis | Approved by FDA on August 30, 2017 to treat acute lymphoblastic leukemia in patients up to 25 years. | Not yet sold or redeemed. |

Note: Table last updated August 31, 2017. GlaxoSmithKline and ViiV Healthcare acquired a PRV for \$130 million and submitted it to the FDA along with the dolutegravir and rilpivirine 2-drug regimen New Drug Application (ViiV Healthcare, June 2017). It is not currently known which pharmaceutical company sold the voucher in this transaction.

Neglected Tropical Disease Voucher Program

Coartem (artemether-lumefantrine)

The first Neglected Tropical Disease PRV was awarded to Novartis in 2009 for antimalarial Coartem Tablets (artemether-lumefantrine). At the time of FDA approval, this drug was approved to treat malaria in more than 80 countries; in support of its U.S. application, Novartis submitted to the FDA 8 of the 20 studies it had sponsored from 1993 to 2007 to support approval of the drug outside the United States. (Kesselheim et al., 2015). Novartis redeemed the voucher in 2011 on canakinumab for gouty arthritis, but the indication was rejected.

Sirturo (bedaquiline)

The second Neglected Tropical Disease PRV was awarded to Janssen Therapeutics in December 2012. Sirturo (bedaquiline) was approved by FDA as part of a combination therapy to treat adults with multi-drug resistant (MDR) pulmonary tuberculosis (TB) when other alternatives are not available. Sirturo was approved under FDA's accelerated approval program based on a surrogate endpoint, in this case the length of time for a patient's sputum to be free of MDR TB. Sirturo carries a boxed warning indicating that the drug can affect the heart's electrical activity, leading to abnormal and potentially fatal heart rhythm. Nine patients receiving Sirturo in clinical trials died (5 from TB) compared with two in the placebo arm (both from TB) (FDA, 2012a).

In July 2017, Janssen received FDA approval for Tremfya (guselkumab), for which it redeemed its PRV to obtain a priority review. The drug is approved to treat moderate to severe plaque psoriasis.

Impavido (miltefosine)

The third Neglected Tropical Disease PRV was awarded to Knight Therapeutics in March 2014 for Impavido (miltefosine) to treat leishmaniasis. Originally developed to treat cancer, Impavido has been marketed outside the United States to treat leishmaniasis since 2004 (Doshi, 2014). Paladin Laboratories acquired the drug in 2008 for \$8.5 million and submitted an application to FDA in 2013 based on data from earlier trials conducted by other companies; when Paladin was sold to Endo International later in 2013, rights to Impavido passed to Knight Therapeutics, the new company of former Paladin chief executive Jonathan Goodman (Doshi, 2014).

Knight Therapeutics sold the voucher to Gilead in November 2014 for \$125 million. Gilead redeemed the voucher on Odefsey, which was approved in March 2016 as a complete regimen drug for HIV-1.

VaxChora (CVD 103-HgR)

The fourth Neglected Tropical Disease PRV was awarded to PaxVax Bermuda in June 2016 for VaxChora (CVD 103-HgR), a vaccine for to prevent cholera for travelers. VaxChora is the only FDA-approved vaccine for cholera. The cholera strain (CVD 103-HgR) was originally developed at the Center for Vaccine Development (CVD) at University of Maryland, Baltimore in the 1980s, and the it went through various trials but the licensing process in the United States was never completed (Sen, 2015). This technology was in-licensed by PaxVax in 2010 (PaxVax, 2015). As of 2012, CVD 103-HgR was previously approved and marketed in six countries under the brand name "Orochol." (PaxVax, 2012).

PaxVax likely sold the PRV to Gilead for approximately \$200 million according to speculation by various sources.¹⁹

Benznidazole

On August 29, 2017, FDA granted approval of benznidazole to treat Chagas disease in children aged 2 to 12 years to Chemo Research S.L. (FDA News Release, 2017b and Pharmacy Times, 2017). This is the first treatment approved in the United States for Chagas disease (Pharmacy Times, 2017).

Chemo Research S.L. was awarded a Tropical Disease PRV upon approval of the benznidazole treatment. Chagas disease is a parasitic infection caused by *Trypanosoma cruzi*. Although its prevalence in the United States is fairly low, Chagas disease is more common among people from Latin America or among the children of women infected in areas in which the parasite is endemic (CDC, https://www.cdc.gov/parasites/chagas/gen_info/detailed.html).

Prior to this approval, benznidazole had been approved by FDA to treat Chagas disease in children aged 2 to 12 years, but was only available from CDC and not in U.S. pharmacies (CDC, https://www.cdc.gov/parasites/chagas/health_professionals/tx.html).

Rare Pediatric Disease Voucher Program**Vimizim (elosulfase alfa)**

The first Rare Pediatric Disease PRV was awarded to BioMarin in February 2014 for Vimizim (elosulfase alfa). Vimizim is the first FDA-approved treatment for Mucopolysaccharidosis Type IVA (Morquio A syndrome), a rare, autosomal recessive lysosomal storage disease. The pivotal trial for Vimizim was launched 17 months before the rare pediatric PRV program took effect (Kesselheim et al., 2015).

¹⁹ See for example <https://seekingalpha.com/article/4008098-priority-review-vouchers-revisited>.

BioMarin sold the voucher to Regeneron and Sanofi in July 2014 for \$67.5 million (Kesselheim et al., 2015). The voucher was redeemed on the PCSK9-inhibitor alirocumab, approved in July 2015 for the treatment of familial hypercholesterolemia.

Cholbam (cholic acid)

The second Rare Pediatric Disease PRV was awarded to Retrophin (formerly Asklepios Pharmaceuticals) in March 2015 for Cholbam (cholic acid) to treat rare bile acid synthesis disorders. Efficacy and safety of Cholbam had been demonstrated in an investigator-initiated trial begun in 1994 (Kesselheim et al., 2015).

Retrophin sold the voucher to Sanofi in July 2015 for \$245 million. Sanofi redeemed the voucher in December 2015 on LixiLan (Soliqua 100/33), a fixed-ratio combination of lixisenatide and insulin glargine for the treatment of type 2 diabetes; the drug was approved by FDA in November 2016.

Unituxin (dinutuximab)

The third Rare Pediatric Disease PRV was awarded to United Therapeutics in March 2015 for Unituxin (dinutuximab), part of a first-line therapy for high-risk neuroblastoma. Unituxin was largely developed by the National Cancer Institute (NCI), with United Therapeutics being selected at a late stage of development to commercialize the drug. NCI synthesized the drug, conducted all preclinical studies, and (manufacturing the drug through the Biopharmaceutical Development Program) conducted clinical trials from 2001 to 2009 (Kesselheim et al., 2015). NCI selected United Therapeutics in 2010 out of more than a dozen companies to commercialize the drug it had developed (United Therapeutics, 2017); this suggests that even 2 years before the Rare Pediatric Disease Voucher Program was authorized, NCI had reason to believe that United Therapeutics intended to commercialize the drug.

United Therapeutics sold the voucher to AbbVie in August 2015 for \$350 million. The voucher has not yet been redeemed.

Xuriden (uridine triacetate)

The fourth Rare Pediatric Disease PRV was awarded to Wellstat Therapeutics in September 2015 for Xuriden (uridine triacetate) to treat an extremely rare eye disorder, hereditary orotic aciduria. FDA approached Wellstat to continue development of the drug when the previous sole supplier discontinued its development program. Four of the 20 known patients in the world received treatment during trials. In addition to the Rare Pediatric Disease PRV, FDA also granted Xuriden orphan drug designation and Breakthrough Therapy designation.

Uridine triacetate is also available as Vistogard, which was approved by FDA just a few months after Xuriden and which is marketed, sold and distributed in the United States by Wellstat's commercialization partner BTG. Vistogard is used to treat adults and children who

receive an overdose of the cancer treatment drugs fluorouracil or capecitabine, or who develop certain severe or life-threatening toxicities within four days of receiving these cancer treatments. Vistogard also received orphan drug, priority review, and fast track designation.

Wellstat negotiated a deal in 2014 to transfer the voucher to AstraZeneca upon FDA approval of Xuriden (BusinessWire, 2015). Details are undisclosed, and the voucher has not yet been redeemed.

Strensiq (asfotase alfa)

The fifth Rare Pediatric Disease PRV was awarded to Alexion Pharmaceuticals in October 2015 for Strensiq (asfotase alfa). Strensiq is the first treatment approved for perinatal, infantile, and juvenile-onset hypophosphatasia, a rare, genetic, progressive, metabolic disease leading to severe disability and life-threatening complications. Alexion Pharmaceuticals acquired Strensiq in 2012 when it bought Canadian biotech Enobia Pharma, which had initially developed the drug. The voucher has not yet been sold or redeemed. Alexion plans to use the voucher on its own drug candidates (Sutter, 2015).

Kanuma (sebelipase alfa)

The sixth Rare Pediatric Disease PRV was awarded to Alexion Pharmaceuticals in December 2015 for Kanuma (sebelipase alfa), the first treatment for lysosomal acid lipase deficiency. Also known as Wolman disease, LAL deficiency typically affects infants in the first year of life, and causes a build-up of fatty material in the gut and other organs, leading to growth failure, cirrhosis, and death in the first year of life. Kanuma is an enzyme replacement therapy for treatment of LAL deficiency. The drug was discovered and developed by Synageva BioPharma, which was acquired by Alexion Pharmaceuticals in June 2015. The voucher has not yet been sold or redeemed.

Exondys 51 (eteplirsen)

The seventh Rare Pediatric Disease PRV was awarded to Sarepta Therapeutics in September 2016 for Exondys 51 (eteplirsen) which treats Duchenne muscular dystrophy (DMD). Symptoms of DMD include degeneration of skeletal and cardiac muscle resulting in loss of function in childhood and adolescence and premature death from respiratory or cardiac failure in the second to fourth decade of life. (FDA, 2016a). Exondys 51 received accelerated

approval²⁰ from the FDA for treating of patients who have a confirmed mutation of the dystrophin gene that is amenable to exon 51 skipping induced by the drug. This mutation affects about 13% of the population with DMD. (FDA, 2016b)

Sarepta Therapeutics (formerly AVI BioPharmaceuticals) discovered Exondys 51²¹ in a collaborative research effort with Ercole Biotech in December 2006 (Adis Insight, 2017), six years before the Rare Pediatric Disease PRV program was created. The Exondys 51 IND was submitted in August 2007. FDA granted Orphan Drug and Fast Track designations shortly thereafter (Serepta Therapeutics, 2016). Exondys 51 is now being sold for \$300,000 a year (Carroll, 2016).

Serepta sold its PRV to Gilead Sciences for \$125 million in February 2017. Gilead likely used this PRV (or one possibly purchased from PaxVax Bermuda) to obtain a priority review for an investigational, fixed-dose combination of bicitegravir and emtricitabine/tenofovir alafenamide to treat HIV. FDA granted the priority review in August 2017.

Spinraza (nusinersen)

The eighth Rare Pediatric Disease PRV awarded to drug sponsor Biogen (under a licensing partnership with drug developer Ionis Pharmaceuticals) in December 2016 for Spinraza (nusinersen) which is indicated for treatment of spinal muscular atrophy (SMA) in children and adults. SMA is a rare and often fatal genetic disease affecting muscle strength and movement (FDA, 2016c). FDA granted Spinraza fast track designation, orphan drug designation, and priority review.

One dose of Spinraza will cost \$125,000, which amounts to \$625,000 to \$750,000 in the first year and \$375,000 in following years (Thomas, 2016). Spinraza was co-developed by Ionis Pharmaceuticals (formerly Isis Pharma) and Dr. Adrian R. Krainer and others at Cold Spring Harbor Laboratory, a non-profit research institution (Bodzo and Myers).

It appears that NIH funding also played a role in the development of some of the key patents related to Spinraza (Love, 2017).

Biogen has not sold or redeemed the PRV, and plans have not been announced.

²⁰ The FDA's accelerated approval pathway approves a drug for marketing based on a surrogate endpoint biomarker – allowing patients to receive the drug ahead of when they typically would have access – while the pharmaceutical company sponsor conducts clinical trials to verify the predicted clinical benefit. Interestingly, FDA would not have the authority to revoke the PRV if the drug does not prove clinical benefit in post-approval trials. (<http://www.raps.org/Regulatory-Focus/News/2016/09/22/25881/Pediatric-Priority-Review-Vouchers-on-the-Chopping-Block-as-Reauthorization-Stalls/>)

²¹ Exondys 51 (eteplirsen) is also known as AVI-4658

Emflaza (deflazacort)

The ninth Rare Pediatric Disease PRV was awarded to drug sponsor Marathon Pharmaceuticals in February 2017 for Emflaza (deflazacort) tablets and oral suspension to treat patients age 5 years and older with DMD. Emflaza is an anti-inflammatory corticosteroid. According to the FDA, corticosteroids are commonly used to treat DMD around the world, but this is the first such approval in the United States (FDA, 2017). In fact, prior to the FDA approval, deflazacort was available in Canada, Europe, and the United Kingdom, and had been imported into the United States for decades by some DMD patients.

Marathon exclusively licensed data from two clinical studies conducted in the past by another company to support its NDA submission in the U.S. Marathon also conducted a full clinical pharmacology program for Emflaza which included eight clinical pharmacology and safety studies and nine preclinical studies (Marathon Pharmaceuticals, 2017). The pivotal Phase 3 study was one of the two studies licensed by Marathon (MDA, 2016). This study was completed in 1995. (Griggs et al., 2016).

Marathon sold Emflaza to PTC Therapeutics in March 2017 for approximately \$140 million plus a milestone payment associated with the drug's sales (Vinluan, 2017). The PRV was not transferred as part of this deal (Staton, 2017).

Brineura (cerliponase alfa)

The tenth Rare Pediatric Disease PRV was awarded to drug sponsor BioMarin in April 2017 for Brineura (cerliponase alfa) for the treatment of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), an extremely rare form of the Batten disease. CLN2 is a fatal neurodegenerative condition that causes children to lose the ability to walk and talk around age 6 and often leads to death between the ages of 8 and 12. BioMarin estimates that about 20 children in the United States are born with the condition each year (BioMarin, 2017). Brineura is an enzyme replacement therapy administered directly to the brain.

On a recent earnings call, BioMarin's CEO said the company has not yet decided how it will use the voucher (Yahoo Finance, 2017). BioMarin sold its first Rare Pediatric Disease PRV for \$67.5 million.

Kymriah (tisagenlecleucel)

FDA awarded a rare pediatric disease PRV to Novartis on August 30, 2017 for tisagenlecleucel to treat patients up to 25 years of age with acute lymphoblastic leukemia "that is refractory or in second or later relapse" (FDA, 2017c, 1).

The treatment is a form of gene therapy that alters a patient's own cells to treat leukemia (Grady, 2017). Kymriah must be prepared using each patient's own cells obtained from a blood draw, then genetically engineered by Novartis to treat the patient's condition (Grady,

2017). The treatment was initially developed by a researcher at the University of Pennsylvania (Grady, 2017).