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4

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Executive Summary

On the thirty-fifth anniversary of the adoption of the Orphan Drug Act (ODA), we describe the enormous changes in the markets for therapies for rare diseases that have emerged over recent decades. The most prominent example is the fact that the profit-maximizing price of new orphan drugs appears to be greater today than it was in 1983. All else equal, this should reduce the threshold for research and development (R&D) investment in an economically viable product. Further, the small size of patient populations for orphan drugs, together with the increasing prevalence of biologics among orphan drugs, have created a set of natural monopoly-like markets in which firms face little competition, even after the end of formal periods of patent protection and market exclusivity. Additionally, the evolving technologies of drug development—in particular, the increasingly common use of auxiliary endpoints in clinical trials and the use of biomarkers for patient selection for treatment—now allow manufacturers to target smaller populations. Taken together, these changes raise doubts about whether the ODA encourages the development of products that otherwise would not have been brought to market—or whether, instead, it simply rewards the producers of inframarginal products. After presenting empirical support for our claims of an evolving marketplace, we discuss the trade-offs associated with reshaping the ODA for the twenty-first century.

I. Introduction

Several countries, including the United States, Japan, and the members of the European Union (EU), have adopted laws and public policies to

encourage manufacturers to commercialize "orphan drugs" that target exceptionally rare diseases. The United States enacted the first orphan drug law in 1983, followed by Japan in 1993, and the EU in 2000 (see table 1). These laws offer special incentives to manufacturers to develop therapies for rare diseases, with rarity defined either by population size (in the United States, an overall population of fewer than 200,000 patients) or prevalence (for the EU, fewer than 5 in 10,000). A number of other countries—including Australia, Korea, and Hong Kong—have adopted similar legislation, but orphan drug laws do not exist in Africa, South America, and most of Asia (Gammie, Lu, and Babar 2015). Many of these countries, however, do have access to products developed in other markets.

The justification for these orphan drug laws is that the existing research and development (R&D), regulatory, and patent systems offer inadequate incentives for manufacturers to invest in the development of drugs for rare diseases. The inadequacy of the incentives stems from the fact that developing new and innovative pharmaceutical products requires enormous up-front and fixed investments that do not meaningfully vary by the size of the prospective market for the drug. If anything, these costs could be larger for smaller market products, where patient recruitment and other costs for clinical trials can be larger. These up-front costs include not only financing R&D activities, but also coping with uncertainty regarding the likelihood of success in achieving regulatory approval and market success.

When markets are large enough, firms are willing to make such fixed risky investments because patent systems, coupled with periods of regulatory exclusivity, provide innovator firms with a period of monopoly power during which they can charge prices that represent a significant margin over manufacturing costs. Ultimately, theory predicts that firms will continue to invest in the development of new products as long as the expected profitability of doing so exceeds the anticipated fixed costs associated with new product development and commercialization.

Expected profits depend on the customers' (health insurers and patients) willingness to pay, the volume of potential users (patients), and the firm's expectations about the nature of competition that will emerge during and after the life of the product's key patent(s). Consequently, therapies that treat a larger number of patients and/or those that are targeted at patients with a high willingness to pay are likely to have larger expected profits. On the other hand, therapies that treat only a small population of individuals (e.g., drugs for rare diseases) or

products that target patients with a low willingness to pay (e.g., products for diseases that are only prevalent in the developing world, such as malaria and other neglected tropical diseases) may not be economically viable (Glennerster and Kremer 2000).

As a corollary, investments in R&D are predicted to stop after the point where the marginal product of an additional dollar invested in new product development is expected to earn risk-adjusted profits that are equal to the fixed costs of R&D for that product. As such, firms are continually evaluating both the set of factors that contribute to development costs and those that affect postmarket profits. Indeed, several empirical studies find that changes to the expected profits of particular drug markets lead to increased R&D expenditures and innovation in those areas (Acemoglu and Linn 2004; Finkelstein 2004; Blume-Kohout and Sood 2013; Dranove, Ody, and Starc 2017; Dubois et al. 2015).

Although the details of laws and policies designed to induce orphan drug innovation differ across countries (see table 1), they typically offer a fixed period of market exclusivity starting at the time of regulatory approval and running concurrently with any patents. The European Union and Japan offer ten years of exclusivity; the United States offers seven years.[1] Because patents already confer on manufacturers the exclusive right to market a given drug, the value of the exclusivity period will depend on the strength and remaining duration of any existing patents. For drugs with strong patents that extend beyond the seven- or ten-year window conferred through *regulatory* exclusivity, the exclusivity period is unlikely to be particularly valuable. For drugs with weak or lapsed patents, however, orphan drug exclusivity can function as a partial substitute for patent protection.

R&D activities related to orphan drugs also receive substantial tax advantages under most orphan drug laws. In the United States, for example, the 1983 Orphan Drug Act (ODA) extends a tax credit for all R&D conducted on a drug that has secured an "orphan drug designation" from the US Food and Drug Administration (FDA). To secure a designation, a manufacturer must submit a request describing the drug and identifying the rare disease that the drug is intended to target.[2] In 2017, the FDA granted an orphan drug designation to 476 potential products, an all-time high and an increase of 43% over the previous year (Karst 2018). Once a drug is designated, the manufacturer can claim tax credits amounting to 25% of any R&D associated with the drug. (The credit was 50% for most of the history of the law, but was reduced as part of the 2017 tax overhaul.)[3] The US Treasury

Table 1
Orphan Drug Legislation in the United States, Japan, and the European Union

Country	Year Adopted	Threshold for Orphan Drug Status	Market Exclusivity from Date of Approval	Financial Support for R&D	Accelerated Approval	Orphan Drugs Approved in 2014*	Total Number of Orphan Drugs Approved through February 2015*
United States	1983	Fewer than 200,000 patients in the United States (6 in 10,000)	7 years	Tax credits of 25% of R&D costs	Yes	40	496
Japan	1993	Fewer than 50,000 patients in Japan (4 in 10,000)	10 years	Reimbursement of up to 50% of R&D costs, plus 6% tax credit	Yes	30	236
Countries of the European Union	2000	Fewer than 5 in 10,000	10 years	Varies across member states	Yes	17	87

Source: Murakami and Narukawa (2016).

Department estimates that $2.3 billion in orphan drug tax credits were claimed in 2017.[4]

Most orphan drug laws also reduce the time and expense associated with securing regulatory approval. Both Japan and the United States, for example, offer "fast-track" approvals for orphan drugs, which may, in turn, lead to longer periods of patent protection through faster regulatory approval processes, given the fixed length of patents. Such regulatory benefits also decrease the fixed cost of bringing products to market.

Thus, existing orphan drug policies both attempt to (a) *decrease the fixed costs* of therapeutic development, as well as (b) *increase the potential profits of successful products* for rare diseases by extending manufacturers' periods of monopoly pricing power. Such policies shift the threshold of profitability for orphan drugs and will therefore increase R&D investments in some otherwise unprofitable products.

Any policy designed to improve the development of therapies for rare diseases requires defining the set of conditions that require additional incentives for drug development. Generally, discussions of orphan drugs focus on the number of patients with a rare disease. The ultimate concern, however, is whether the expected profitability of the product exceeds the likely development costs. Recognizing this fact, the ODA originally focused on *economic viability*, rather than solely on the size of the patient population. The former is a focus that more directly matches the business decisions that pharmaceutical firms face, although the latter provides a clear and straightforward decision rule for policy implementation.

In its original incarnation in 1983, the ODA defined a rare disease as, "any disease or condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" (21 CFR Part 316). In addition, the ODA was written to leave open the possibility that the definition of such settings might change over time, specifically noting that, "determinations under the preceding sentence with respect to any drug shall be made on the basis of facts and circumstances as of the date the request for designation under this subsection is made."

One year after the passage of the ODA, however, Congress revisited the definition of a rare disease and established a patient population threshold of 200,000. The Office of the Inspector General of the Department of Health and Human Services has said that "[t]he threshold was

an arbitrary ceiling based on the estimated prevalence of narcolepsy and multiple sclerosis" (Office of the Inspector General 2001). This threshold remains in place today, despite a variety of changes to the drug-development process, demographics, and therapeutic markets that are likely to influence the decisions of firms regarding whether to invest in a therapy for a rare condition. For example, the population of the United States has increased by over 90 million individuals since the definition's establishment. Holding the incidence of disease and other factors constant, this population increase has effectively decreased the number of conditions that could qualify for an orphan designation. Other factors, however, cut in the opposite direction, creating new product development opportunities for niche markets.

In aggregate, the passage of the ODA has been associated with an increase in the development of products for diseases that are known to have patient populations below 200,000 (Yin 2008). In the decade preceding 1983, just 10 drugs were approved to treat orphan conditions in the United States. However, in the decade spanning 2006 to 2015, 274 orphan drugs were approved (Karst 2018). Similar increases in the pace of approvals have been seen in the European Union and Japan, with most of the growth driven by the development of new drugs for rare cancers. Some of these drugs represent novel treatments; half of all orphan drugs approved in the United States are first in their class, a rate much higher than that seen among nonorphan drugs (Miller and Lanthier 2016). Ivacaftor (Kalydeco), for example, offers life-changing relief for those suffering from certain subtypes of cystic fibrosis, and imiglucerase (Cerezyme) and eliglustat (Cerdelga) treat variants of Gaucher disease, a debilitating condition that occurs when an enzyme responsible for fat metabolism malfunctions.

But providing incentives for the development of new drugs involves a series of trade-offs. Most obviously, there is a direct cost of foregone public revenue as a result of tax credits. A second cost arises from the regulatory exclusivity periods. This exclusivity may decrease competition and can increase drug spending, effectively transferring surplus from taxpayers (who finance Medicare and Medicaid) and the privately insured to manufacturers.[5] In addition, depending on the elasticity of demand for the product, this exclusivity period can decrease welfare by decreasing output in these markets.

The size of the second transfer and potential welfare loss effectively depends on the nature of expected competition for the particular indication. That, in turn, is a function of the patent status of the product.

For example, a product lacking exclusivity but covered by at least one strong patent would expect little competition to emerge during the patent life. A regulatory exclusivity period overlapping with the patent term(s) would thus result in negligible transfers. However, for drugs that lack (strong) patents, or for drugs whose patents expire during the ODA-granted exclusivity period, the additional market exclusivity provided by the ODA has the potential to lead to relatively large transfers.

Concretely, the share of orphan drugs with exclusivity periods that extend beyond a drug's patent life has been falling; a recent study found that among orphan drugs approved from 1985 through 1994, 50% had exclusivity periods that outlasted the product being covered by any patent, with this share falling to 35% for orphan drugs approved from 1995 through 2004, and just 18% for orphan drugs approved between 2005 and 2014 (Sarpatwari et al. 2018). These data are suggestive of a decrease in the average benefit of ODA-granted exclusivity. However, the underlying strength of the patents covering products in these time periods is unclear. For example, this increase in the share of products receiving the benefits of exclusivity that are under patent could reflect an increase in ancillary patents that offer little true protection from competition.

Even if the relative benefits of exclusivity have declined over time, there are still a number of criticisms related to the size of ODA-driven transfers. Broadly speaking, these fall into four categories:

1. Changes in *pricing dynamics* have resulted in higher average prices for drugs overall, and for orphan drugs in particular. By decreasing the population size threshold for an economically viable product, those dynamics have weakened the case for additional incentives targeted at orphan drugs.

2. The small size of patient populations for orphan drugs, together with the approval of an increasing number of complex biologics, has created a set of *natural monopoly-like market segments* in which firms face little competition, even after the end of patent protection and market exclusivity.

3. Changes in the *technology of drug development*, such as the use of auxiliary or "surrogate" endpoints, and biomarkers for selecting patients for clinical trials, have allowed pharmaceutical manufacturers to target increasingly smaller patient populations, including subpopulations of more common conditions.

4. Firms increasingly seek *multiple orphan drug indications* for a single product, sometimes even when that product has already been approved for one or more nonorphan indications. In the latter case in particular, the orphan drug laws do not serve their purpose of *spurring development* of products for which there would not otherwise be a viable market. They could, however, provide benefits by increasing knowledge about additional novel uses for existing products or efficacy and safety for existing uses of products.

The common thread among all of these concerns is the degree to which the ODA currently provides incentives for the development of products that otherwise would not have been brought to market, versus simply rewarding the producers of inframarginal products.

Overall, firms respond to the incentives created by both the market and policymakers. As such, if existing policy rewards inframarginal products, profit-maximizing firms will claim those benefits. Similarly, if existing policy is unable to provide adequate incentives for firms to invest in certain products, it should not be surprising to see that such products are not developed. In fact, well-crafted policy should assume firms will act rationally, and as such, public policies should be designed to provide incentives that recognize this aspect of firm behavior. With such incentives, policymakers can strive to avoid the proverbial "folly of rewarding A, while hoping for B." We believe that the thirty-fifth anniversary of the ODA's passage and the current period of significant technological change both mark an important time to reflect on the ODA's performance.

We begin by noting that the prices paid for products with orphan approvals have grown substantially since the passage of the ODA. Table 2 contains descriptive statistics for products based on their orphan status from a major claims database (see below for a more detailed description). Aggregated summary statistics are provided for the periods 1995–2005 and 2006–2016. Like many efforts to understand pharmaceutical pricing, the underlying data for these drugs do not provide a complete picture of the net prices paid. But the data nonetheless point to increasing prices for orphan products and a shift in the composition of spending on branded products toward those holding this status. For example, from 1995 to 2005, 7.3% of brand name drug spending went toward orphan drugs. For the period from 2006 to 2016, that figure rose to 20.6%.

The prevalence cutoff for defining a rare disease was first established nearly 35 years ago, and at the time was based on the size of patient

Table 2
Descriptive Statistics for Orphan and Nonorphan Drugs

	1995–2005		2006–2016	
	Nonorphan Drugs	Orphan Drugs	Nonorphan Drugs	Orphan Drugs
All Approved Brand Name Drugs[a]				
Number of Patients				
Mean	7,612.3	1,073.7	7,398.9	1,551.7
Median	167	0	74	12
Spending ($000s)				
Mean	1,501.1	1,162.4	2,840.1	5,542.5
Median	20.8	0	28.3	8.1
Total	22,920,415	1,797,131	60,330,307	15,635,296
Brand Name Drugs in Contemporary Use[b]				
Number of Patients				
Mean	9,469.1	1,743.7	10,494	2,258.7
Median	526	79.5	569	67
Spending ($000s)				
Mean	1,867.2	1,887.7	4,028.2	8,067.7
Median	66.5	79.5	256.9	462.7
Total	22,920,415	1,797,131	60,330,307	15,635,296

Source: OLDW Pharmacy Claims.
[a] Summary statistics are calculated over drug-years. For example, mean nonorphan population size for 1995–2005 represents the average number of patients for approved nonorphan drugs over that 11-year period.
[b] Drugs in contemporary use refers to drugs with one or more claims in a given year. We include only drug-years that fit this criterion in the lower panel. Population size and spending are set to zero for drugs in years that 10 or fewer patients were treated.

populations for a subset of diseases that were believed to lack sufficient incentives for pharmaceutical innovation. Over the past three and a half decades, there have been a variety of technological advances in the process of researching and developing drugs. For example, the increasing use of genomic and proteomic biomarkers now allows for R&D in a larger number of potential therapeutics for small, highly targeted patient populations (Chandra, Garthwaite, and Stern 2017).

Suggestive evidence of a change in the underlying technology and the ability to identify new orphan populations can be seen in the quickening pace of orphan drug designations in recent years. To illustrate, Figure 1 shows that prior to the completion of the Human Genome Project in 2003, the number of annual orphan drug designations was relatively constant, sitting below 100. Beginning in that year, there was a marked increase in the number of orphan drug designations granted by the FDA, and now there are several hundred designations granted
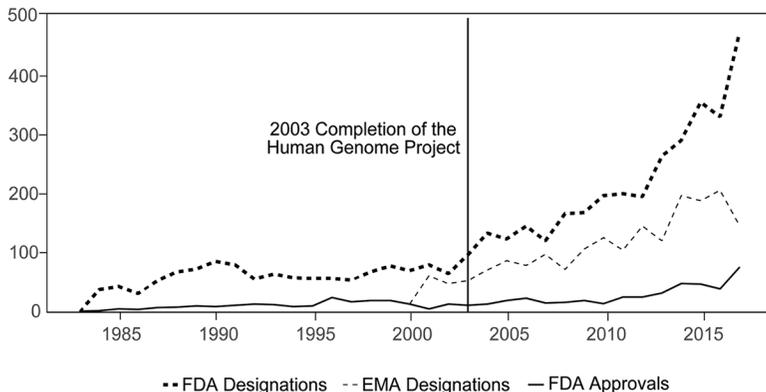
Fig. 1. Orphan designations and approvals 1985–2017
Sources: Drugs@FDA and European Medicines Agency.

per year. Advances in biomarker technology have allowed for more precise definitions of patient populations, creating more opportunities for successful orphan drug applications (Kesselheim, Treasure, and Joffe 2017). For example, from 2009 to 2015, 16% of orphan drug approvals were based on biomarker-defined subsets of diseases. To the extent that these biomarker-defined products can also be more highly reimbursed, they may represent products that could be profitably brought to market without the additional incentives provided by the ODA.

We also examine the degree of competition that should be expected for firms over the lifetime of the product. By delaying the onset of generic competition, the seven years of market exclusivity for orphan drugs is meant to provide additional profits to induce development. At least in some drug markets, however, this protection may be redundant. In particular, the generic market for many rare diseases is insufficiently attractive to encourage entry from generic manufacturers. As such, may rare-disease markets exhibit all the characteristics of natural monopoly markets.

Finally, we examine the question of multiple orphan indications for products, including products originally approved for (more) common indications. One might criticize the granting of orphan indications for already approved and marketed products as rewards for inframarginal activities that may appear to conflict with the spirit of the ODA. On the other hand, truly novel uses for existing products that target rare conditions could require meaningful investments that might not be made without additional nonmarket incentives from the government.

Further, with respect to the use of drugs for diseases other than their first indication(s), physicians can prescribe FDA-approved drugs "off-label" (i.e., for indications other than those on the drug's official label). Therefore, if a drug is found to be efficacious for something other than its approved indication(s), it can often be used by patients with those other conditions. However, physicians treating patients off-label will typically lack high-quality, FDA-verified clinical trial evidence documenting the drug's efficacy in the relevant population, and payers may be resistant to reimburse treatment (particularly for expensive drugs) for individuals with an off-label condition. In the extreme, drugs that require "preauthorization" in order to be reimbursed by payers may not be feasible to use off-label. In these settings, establishing additional indications—for both orphan and other populations—will improve patient welfare, but this type of welfare improvement is distinct from questions regarding a drug's economic viability.

Taken together, accumulated data and experience provide evidence that the market for developing treatments for rare diseases has materially changed since the passage of the ODA 35 years ago. To further examine these issues, we examine the expanding role of orphan drugs, the empirical evidence for the four concerns about the efficiency of the ODA listed above, and conclude with a discussion of the relevant policy trade-offs.

II. The Changing Pricing Dynamic for Orphan Drugs

A common belief is that without orphan drug laws, market incentives would be inadequate to encourage drug manufacturers to develop drugs that can only be sold to a restricted patient population. Evidence to support this view, however, is elusive, and primarily relies on studying the emergence of new therapeutics to treat rare conditions before and after the passage of the ODA. These data provide suggestive evidence of the ODA's impact on drug innovation at the time of its passage. Changing market dynamics over the past 35 years mean that even this suggestive evidence provides little information on the *causal* impact of the ODA on development incentives in today's environment.

As noted above, firm decisions about R&D investments are driven by the expected costs and profits of a new product. While the expected market size for a new drug is a component of expected profits, a small market does not necessarily imply that firms will decline to invest in a development project. A firm may anticipate a low volume of sales

due to a small target population, but it may still be willing to invest if it anticipates that insurers will pay a sufficiently high price for the units they do sell. Consider the market for cystic fibrosis therapeutics. The overall patient population is quite small, numbering 30,000 in the United States and 4,000 in Canada. Furthermore, as scientific knowledge of the disease has progressed, researchers have identified progressively smaller subpopulations of patients that can be treated. One orphan drug, ivacaftor (Kalydeco), treats individuals with cystic fibrosis that have G551D mutation—a group comprising just 4 to 5% of the total cystic fibrosis population. Yet the drug's manufacturer, Vertex, reported $700 million in revenue from Kalydeco in 2016, and an additional $980 million for its other cystic fibrosis product, Orkambi (Vertex 2017).

The ability to charge high prices is not limited to cystic fibrosis products. In the United States, the median price of an orphan drug in 2015 was nearly US$100,000 per year—almost 20 times the median price of a nonorphan drug—and some drugs cost much more (EvaluatePharma 2015). Eculizumab (Soliris), for example, is used to treat an extremely rare blood disease and costs about $440,000 each year. Prices for orphan drugs are somewhat lower in the European Union and the rest of the world, but are still high relative to conventional drugs (Gammie et al. 2015). In 2014, at least eight orphan drugs had annual worldwide sales exceeding $1 billion (Table 3); Roche reported $6.9 billion in 2014 sales of the highest-grossing orphan drug, rituximab (Rituxan) (Roche Group 2014).

Even with exclusive marketing rights, manufacturers can set high prices only because patients, governments, and private insurers have been willing to pay them—directly (e.g., in the case of many US payers) or indirectly (e.g., through tax subsidies). In many developed countries, demand for orphan drugs is inelastic, meaning that it is relatively insensitive to changes in price. Five features of orphan drugs contribute to these dynamics.

First, orphan drugs are often developed for conditions for which there are few effective treatment options. Especially for first-in-class drugs, payers are particularly unlikely to be unable to substitute cheaper therapies. Relatedly, those afflicted with an orphan disease are sympathetic and supported by well-organized patient advocacy organizations, including the National Organization for Rare Disorders in the United States (NORD) and the European Organization for Rare Diseases (EURORDIS) in the European Union. It may, as a result, be politically untenable or undesirable for a payer to refuse coverage for a

promising new therapy on the grounds of cost. Both factors reduce the price elasticity of demand and consequently may increase the markup charged by the manufacturer.

Second, given small patient populations in equilibrium, firms will only invest in R&D for orphan products that target patients with a relatively high willingness to pay for treatment. As a result, the ultimate set of commercialized therapeutics is selected by business strategists based on demographics (e.g., age) and the severity of the underlying conditions that they target. This selection manifests itself in higher average prices for these conditions that are not *directly* a function of their orphan status.

Third, a small number of afflicted patients means that the cost of any one orphan drug may not severely strain a health system. High prices for relatively common drugs create two sets of externalities for the drug market. First, they can increase the premium for insurance and decrease purchases of that product by liquidity-constrained customers (Besanko, Dranove, and Garthwaite 2016). Second, high drug prices for more common products can attract greater regulatory scrutiny, which might invite policy intervention (e.g., price controls) that would affect the broader market. Both of these factors would have a greater impact on the profitability of firms selling a portfolio of products, because they would affect the profitability of products beyond the one with the high price. In other words, a manufacturer that only sells one or two orphan drugs may find it optimal to charge higher prices than a manufacturer with one or two orphan drugs as well as a portfolio of more commonly used drugs with higher budget impact. This fact is important given that, as the biotech market has evolved, a large number of relatively small firms have assumed primary responsibility for early-stage drug development. Even if big manufacturers eventually purchase these products, the purchase price (and the resulting optimal retail price) will reflect the forgone value to the smaller firms of bringing the product to market themselves.

Fourth, and looking forward, the advent of precision medicines allows manufactures to charge even higher prices because of the ability to price discriminate through "indication-based pricing" of the type deployed by Novartis for its new CAR-T therapy.[6] If willingness to pay for a drug varies by the indication that it is used for (either because of the health value created or the absence of alternative therapies), manufacturers would be able to charge higher prices for these uses and lower prices in less valued indications. That kind of price discrimination will

Table 3
Worldwide Top 20 Selling Orphan Drugs in 2020

Rank	Product	Generic Name	Company	Phase (Current)	Pharmacological Class	WW Product Sales ($m) 2014	2020	CAGR (%)
1	Revlimid	lenalidomide	Celgene	Marketed	Immunomodulator	4,980	10,058	+12
2	Opdivo	nivolumab	Bristol-Myers Squibb	Marketed	Antiprogrammed death-1 (PD-1) MAb	6	8,192	+233
3	Soliris	eculizumab	Alexion Pharmaceuticals	Marketed	Anticomplement factor C5 MAb	2,234	5,414	+16
4	Keytruda	pembrolizumab	Merck & Co.	Marketed	Antiprogrammed death-1 (PD-1) MAb	55	5,297	+114
5	Rituxan	rituximab	Roche	Marketed	Anti-CD20 MAb	7,547	5,117	-6
6	Orkambi	lumacaftor; ivacaftor	Vertex Pharmaceuticals	Marketed	Cystic fibrosis transmembrane conductance regulator (CFTR) corrector	—	5,051	n/a
7	Imbruvica	ibrutinib	AbbVie	Marketed	Bruton's tyrosine kinase (BTK) inhibitor	—	2,982	n/a
8	Imbruvica	ibrutinib	Johnson & Johnson	Marketed	Bruton's tyrosine kinase (BTK) inhibitor	55	2,712	+91
9	Esbriet	pirfenidone	Roche	Marketed	Tumor necrosis factor alpha (TNFa) and transforming growth factor-beta (TGF-β) inhibitor	48	2,492	+93
10	Tasigna	nilotinib hydrochloride monohydrate	Novartis	Marketed	BCR-ABL tyrosine kinase inhibitor	1,529	2,331	+7

11	Pomalyst	pomalidomide	Celgene	Marketed	Immunomodulator	680	2,060	+20
12	Alimta	pemetrexed disodium	Eli Lilly	Marketed	Thymidylate synthase inhibitor	2,792	2,019	−5
13	Gazyva	obinutuzumab	Roche	Marketed	Anti-CD20 MAb	54	1,932	+82
14	Advate	factor VIII (procoagulant)	Baxalta	Marketed	Factor VIII	2,348	1,918	−3
15	Kyprolis	carfilzomib	Amgen	Marketed	Proteasome inhibitor	331	1,857	+33
16	Obeticholic acid	obeticholic acid	Intercept Pharmaceuticals	Filed	Farnesoid X receptor (FXR) agonist	—	1,827	n/a
17	Yervoy	ipilimumab	Bristol-Myers Squibb	Marketed	Anticytotoxic T lymphocyte associated protein 4 (CTLA4) MAb	1,308	1,723	+5
18	Ofev[a]	nintedanib	Boehringer Ingelheim	Marketed	Tyrosine kinase inhibitor	5	1,674	+164
19	Cyramza	ramucirumab	Eli Lilly	Marketed	Anti-VEGF-2 MAb	76	1,655	+67
20	Sprycel	dasatinib	Bristol-Myers Squibb	Marketed	Tyrosine kinase inhibitor	1,493	1,646	+2
	Other					71,487	109,870	+7
	Total					97,026	177,827	+10.6

Source: EvaluatePharma (2015).

Notes: Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates. Worldwide sales represent sales for all indications. All sales analysis based on EvaluatePharma's clean "orphan" subset of products, as defined in the overview section.

[a] Forecast based on a single broker model.

require that manufactures know what indication a drug is being deployed for. While such indication-based pricing is not yet widely used, the possibility of more widespread use would be facilitated by the future establishment and validation of genomic and proteomic biomarkers for diseases (see Chandra and Garthwaite (2017) for a discussion of indication-based pricing). When the Orphan Drug Act was originally passed, virtually no such biomarkers existed, making indication-based pricing infeasible. In recent years, however, knowledge about biomarkers has improved rapidly. Absent the ability to practice indication-based pricing, manufacturers would charge a common price that reflects the pooled valuation of the drug across high- and low-value conditions. But in a setting where manufacturers can charge higher prices for the drug when used for a rare disease (either because of better effectiveness or higher willingness to pay), it is not clear that the drug will need the same amount of protection from competition in order to be brought to market.[7]

Finally, the 2010 Patient Protection and Affordable Care Act (ACA) increased the market demand for all drugs. Health insurance increases demand for therapeutics (Baicker et al. 2013; Finkelstein et al. 2012) and the ACA was, first and foremost, an insurance expansion. The ACA also prohibited insurers from charging higher prices to sick patients and did away with annual and lifetime caps on insurance benefits. These reforms were particularly valuable for privately insured patients, who needed access to high-cost medicines, including orphan drugs. The ACA thus helps to fuel investment into R&D for orphan drugs by increasing demand for these therapies over the course of a patient's life.

In summary, the combination of longer effective patents, greater price inelasticity, the increasing use of prognostic and diagnostic disease biomarkers, and upticks in consumer demand will increasingly enable drug manufacturers to aggressively price orphan drugs. Market incentives in the *absence* of additional ODA-based provisions are thus increasingly likely to be adequate to foster the development of many orphan drugs. To be sure, *fewer* orphan drugs would be developed in the absence of special treatment of such medicines. However, for those drugs that were developed, competition from generics and biosimilars would arise earlier in some cases (see above). Researchers have struggled to discern the magnitude of firm response and to disentangle it from the response to changes in market conditions (Kesselheim 2011). At a minimum, the relative importance of orphan drug laws for the extensive margin of new drug development has waned as the prices for orphan drugs have climbed.

III.   Data

To identify orphan drugs and their approved labeled indications, we use data from the FDA's online database of Orphan Drug Designations and Approvals.[8] We classify each drug with at least one orphan designation that resulted in an approved indication as of December 31, 2017, as an orphan drug. Then, for each orphan drug, we use data from the Drugs@FDA database to determine all of each orphan drug's approved indications and the respective approval dates. This includes both orphan and nonorphan indications. For example, etanercept (Enbrel) was originally approved to treat rheumatoid arthritis, a common condition that affects about 1.5 million people in the United States,[9] but later received an orphan indication to treat polyarticular juvenile idiopathic arthritis, a rare form of arthritis in children. Using this data on all orphan drug indications, we classify each orphan drug as a "pure" orphan drug (having only orphan indications) or a "mixed" orphan drug (having both orphan and nonorphan indications). For mixed orphan drugs, we additionally classify each drug by approval sequence: whether the drug's first indication was orphan or nonorphan, or whether orphan and nonorphan indications were simultaneously approved. This methodology allows us to broadly reproduce the summary statistics on orphan drugs included in the IQVIA Institute's (formerly IMS Institute's) October 2017 report on orphan drugs in the United States.[10]

We then create a comparison group of brand name nonorphan drugs using data on approved drugs from Drugs@FDA, including detailed information on brand names, active ingredients, and application numbers. Because the methodology we employ to define orphan drugs groups together multiple formulations of a drug with distinct application numbers (e.g., one drug approved under separate applications as an injection and an oral tablet), we adopt a similar approach for nonorphan drugs, clustering nonorphan drug formulations together according to their approved brand name. Then, to determine which brand name drugs faced generic competition, we flag whether any generic drug—as indicated by approval of an Abbreviated New Drug Application (ANDA)—shared an active ingredient.

To track drug spending and utilization, we employ data from the OptumLabs® Data Warehouse (henceforth OLDW). This database comprises retail and mail-order pharmacy claims and inpatient and outpatient medical claims filed by beneficiaries of a large U.S. health plan between 1993 and 2017. We restrict the data to include only claims filed

by commercial-line insurance beneficiaries—omitting beneficiaries that file claims through Medicare Part D coverage. Furthermore, we only consider claims from beneficiaries who are enrolled in both pharmacy and medical coverage through the health plan. For each pharmacy claim, we calculate the total expenditure as the sum of the out-of-pocket expenditure and the health plan expenditure. This notably does not include expenditures by third-party payers nor rebates from drug manufacturers to insurers. This lack of rebates is more concerning when we discuss overall spending or relative spending across products and categories. However, the absence of rebate data likely introduces little bias when we examine spending across indications for the same product.

The main limitation of using claims data from any source is that, due to billing patterns, it is difficult to isolate drug spending that occurs in the course of inpatient or outpatient medical treatment (such as chemotherapy medications), resulting in understated sales of these types of drugs. To mitigate this issue, we capture drug spending only from retail and mail-order pharmacies and then focus our drug-level analysis on a few therapeutics that are both economically significant and widely distributed in the pharmacy setting. For each of these, we track what patients used them to treat by leveraging medical claims data to search for diagnoses prior to a patient's first prescription. For each of the drug's FDA-approved indications, we flag whether the patient has a diagnosis corresponding to that indication in the year prior to its initial prescription. If so, we flag all of that patient's uses of the drug as uses for that indication. For example, if a patient is prescribed Humira on December 31, 2016, and was diagnosed with Hidradentitis Suppurtiva (HS) on January 1, 2016, then all prescriptions filled for Humira for that patient are coded as being used to treat HS.

IV.   Orphan Drug Markets and Natural Monopolies

Because orphan markets are by nature small, they are less appealing for entry by generic and biosimilar manufacturers after orphan exclusivity expires. In a setting without generic or biosimilar entry, the manufacturer of an orphan drug will remain a monopolist for many years—long after relevant patents and exclusivity periods have expired. These natural-monopoly-like conditions are most likely to emerge when the expected economic profitability of a follow-on entrant is small. This may be particularly true in the case of biologic drugs—an increasingly large share of orphan drugs—because both the fixed costs and unit

costs of manufacturing are higher for such products, and in other contexts, biosimilar entry has been linked to the effective market size (Scott Morton, Stern, and Stern 2018). Where competition does not emerge, even a manufacturer that has spent billions on R&D for a drug that treats just 10,000 patients a year will be more likely to recoup its costs given the indefinite lifetime of the effective monopoly period in which to do so. In such a setting, the ODA's exclusivity period is of little value to a manufacturer. Tax credits, however, will represent a pure transfer from taxpayers to the manufacturer, rather than a necessary incentive to allow a product to cross the profitability threshold. Thus, the potential contestability of a drug market is a key to understanding whether the ODA is necessary for inducing innovation (on the extensive margin of whether or not a drug comes to market) versus a setting in which it reflects an unnecessary transfer.

Past experience in the generics industry can help us understand how the manufacturer of an original, branded drug may benefit from a lack of contestability. A recent study, for example, estimates that a drop from three to two generic manufacturers in a market is associated with an increase in prices of as much as 37%; in many markets, there is only one manufacturer, which could price like a monopolist if it believes that it is not in a contestable market (Berndt, Condi, and Murphy 2017). All else being equal, smaller markets attract fewer competitors, meaning that meaningful generic competition is unlikely to emerge to drive down prices in those markets, unlike in larger markets. The importance of various measures of market size in predicting follow-on competition has been observed in the early European experience with biosimilars (Scott Morton, Stern, and Stern 2018). A recent report from the US Department of Health and Human Services (HHS) underscores the concern: generic drugs with a 1,000%+ price increase were in markets that accounted for 0.03% of the overall number of generic prescriptions (HHS 2016). In those markets that accounted for 21% of overall generic prescriptions, drug prices increased a relatively modest 1% to 20%.

In the orphan drug space, a branded manufacturer (or in the case of biologics, reference product manufacturer) can sometimes exploit the link between high prices and low market contestability. Generic and biosimilar manufacturers will recognize that their entry into a small orphan drug market will prompt the branded manufacturer to drop its price to maintain market share. An already small market could therefore become even less profitable on a per-patient basis, potentially

Table 4
Average Utilization at Peak by Presence of Generic Competition

	Average Number of Patients in Peak Year	
	Approved ANDA	No ANDA
Nonorphan drugs	32,069	22,542
Pure orphan drugs	2,316	1,035

Source: OLDW Pharmacy Claims.

eliminating the expected value of entering the market to a generic or biosimilar manufacturer. These manufacturers may thus choose not to enter, leaving branded manufacturers to behave as monopolists. Crucially, the test for contestability is *not* the actual number of generic manufacturers with the technical means to produce competitor drugs, or the existing number of competitors. Instead, markets are considered contestable based on the number of manufacturers that *could* rationally enter. If that number is small—whether due to small market size or high production costs that prevent manufacturers from achieving minimum efficient scale—the original manufacturer will remain a natural monopolist, allowing it to reap the gains of monopoly pricing well beyond the officially granted exclusivity period.

Tables 4 and 5 illustrate the reality of natural monopolies for orphan drugs by comparing the average number of patients in a drug's peak year of use for orphan and nonorphan drugs. This number was slightly greater than 1,000 patients in the data on orphan drugs where no generic entered, and unsurprisingly, more than twice as large for orphan markets where generics entered. This provides suggestive evidence that generic versions of orphan drugs enter the market in situations in which the potential market/patient population is larger. Table 5 shows that about 50% of nonorphan drugs approved since 1984 face generic competition. This number is just 27% for orphan drugs, and 26% for pure orphan drugs (those that do not also have nonorphan indications). In other words, almost three-quarters of orphan drugs do not face generic competition.

These types of pricing dynamics and concerns about the limits of competition were not as well understood in 1983 and 1984, nor were they directly incorporated into competition policy. Indeed, the Drug Price Competition and Patent Term Restoration Act (often referred to as the "Hatch-Waxman Act" after Senators Henry Waxman of California and Orrin Hatch of Utah, who sponsored the act), which established

Table 5
Drugs Facing Generic Competition

	Drugs with Generic Competition	All Eligible Drugs[a]	Percent with Generic Competition
Nonorphan drugs	647	1,285	50.4
Small molecule nonorphan drugs	647	1,263	51.2
Orphan drugs	78	286	27.3
Pure orphan drugs	54	212	25.5
Small molecule pure orphan drugs	54	165	32.7

[a] Eligible drugs comprise all drugs that were approved after 1984, the year the Hatch-Waxman Act created the Abbreviated New Drug Application (ANDA) approval pathway for generic drugs, and before 2011 so that each eligible drug has been approved for seven years as of the cutoff date of December 31, 2017.

the contemporary system of generic drug regulation, did not pass until September 1984.[11]

V.   Changing Technology and Producing Orphan Drugs

After taking all factors into account, many orphan drugs have the potential to cost less to develop than nonorphan drugs of the same type (e.g., small-molecule drugs or biologics). There are a number of reasons for this. On average, clinical trials for orphan drugs enroll 34% as many patients, drugs are approved about three months earlier, and are approved at a higher rate relative to nonorphans (EvaluatePharma 2015; Thomas et al. 2016). Further, studies of neurology and oncology drugs indicate that orphan drugs are often approved on the basis of lower-quality clinical trials than conventional therapies (Mitsumoto et al. 2009; Kesselheim, Myers, and Avorn 2011). These advantages are strengthened by R&D tax credits to innovator firms, which further reduce the costs of developing orphan medications. That said, despite these advantages, products for very rare conditions could be quite costly to bring to market, even with faster and cheaper (lower-quality) trials, because exceptionally small target patient populations could mean difficulties in recruiting a suitable number of patients to demonstrate safety and efficacy.

The cost of bringing new therapeutics, including orphan drugs, to market may also fall with the use of "surrogate" or auxiliary endpoints in clinical trials. Trial endpoints are simply the ex ante selected measurements of patient outcomes in a trial. Surrogate endpoints are

intermediate measures that can be used when the clinical outcomes of interest may take a long time to study, or in cases where the clinical benefit of improving the surrogate endpoint, such as controlling blood pressure, is well understood. While ultimate clinical endpoints (such as overall survival from cancer or AIDS) are what matters to patients, the FDA sometimes allows surrogate endpoints (such as progression-free survival among cancer patients or HIV viral load in a patient's blood among HIV-positive patients) to serve as a proxy in approving drugs, allowing clinical trials for new therapies to be completed more quickly (FDA 2017). Surrogate endpoints typically take the form of "biomarkers"—measurable characteristics of a patient, such as blood pressure or tumor growth.[12] The use of surrogates is likely to accelerate with the adoption of the 21st Century Cures Act, which makes it easier for the FDA to approve drugs based on surrogate endpoints and even observational data. Given the profiles of rare disease and the increasing prevalence of rare cancers among them, orphan drugs will be increasingly likely to be brought to market through clinical trials that rely on surrogate endpoints (Stern, Alexander, and Chandra 2018).

Indeed, biomarkers may be valuable even when they cannot yet be used as surrogate endpoints in registered clinical trials (e.g., because the FDA has not yet "qualified" them).[13] For example, biomarkers can be used in the early phases of research to make go/no-go decisions about drug development. As such, they affect the allocation of resources through the drug-development cycle. In this setting, they may be especially useful in the development of orphan drugs. To see why, consider two types of biomarkers. *Diagnostic biomarkers* are "used to detect or confirm presence of a disease or condition . . . or to identify individuals with a subtype of the disease" (FDA-NIH 2016). These biomarkers can determine whether a patient has a particular disease subtype for trial eligibility. *Prognostic biomarkers* are "used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest," as well as "to identify individuals who are more likely . . . to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent."[14] The use of diagnostic and prognostic biomarkers can improve trial eligibility screening, thereby reducing the likelihood of trial failure. To the extent that orphan diseases have a genetic component to them (e.g., Tay-Sachs disease or Usher syndrome) and treatments for these diseases are built on the basis of a better scientific understanding of
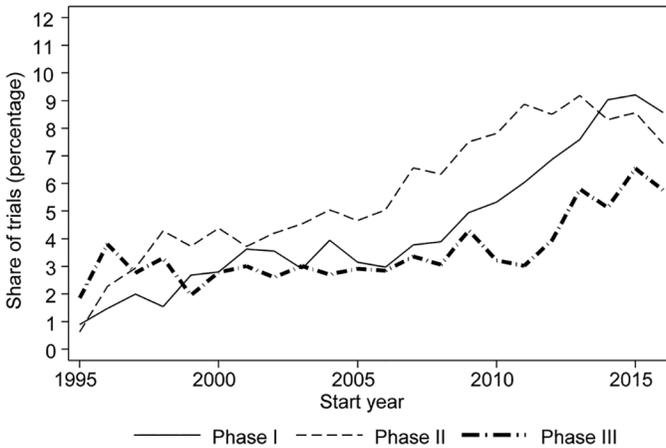
Fig. 2. Share of clinical trials using precision medicine biomarkers
Source: Chandra, Garthwaite, and Stern (2017).

these genetic linkages, advances in biomarkers and their use in clinical research may reduce costs associated with R&D for these diseases.[15] Figure 2 highlights the growth of use of such biomarkers in US clinical trials in recent years (see Chandra, Garthwaite, and Stern (2017) for additional discussion of the use of biomarkers in clinical trials).

We further note that improvements in clinical trial design, such as Bayesian adaptive trials, coupled with the use of biomarkers for efficient patient selection, may reduce trial sizes and durations further. Bayesian adaptive platform trials, for example, allow investigators to relax some of the constraints of traditional clinical trials. In traditional trials, uncertainty about differences across disease subgroups, dosing, treatment duration, or treatment sequencing, can lead to a failed trial. In an adaptive trial design, differences across treatment regimens and differences in efficacy across subpopulations of a disease can be teased out when subpopulations are prespecified. Such trial designs are expected to improve the overall efficiency of clinical research and new drug approval for biomarker-defined subpopulations of diseases, and may be particularly well-suited to identify therapeutic effects in rare diseases with delineable orphan populations (Barker et al. 2009; Berry, Connor, and Lewis 2015; Berry 2015). Exclusivity periods adopted in an earlier era could not, and did not, take into account these advances in trial design.
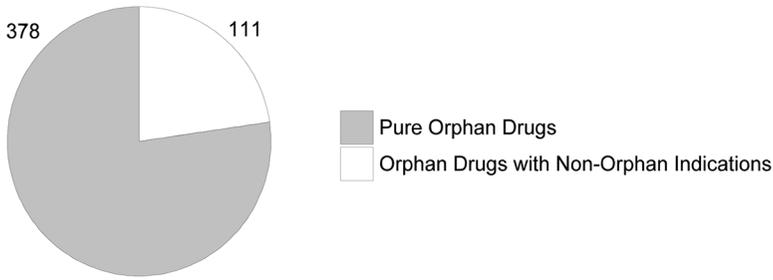
Fig. 3.   Approved orphan drugs
Source: Drugs@FDA.
Note: Only indications approved before January 1, 2018, are included.

VI.   Multiple Orphan Indications per Product

Looking past the inelastic demand for orphan drugs, the risk of natural monopoly, and the rise of precision medicine, drug manufacturers may also "game" features of the ODA for financial benefit. One common complaint involves firms receiving a subsequent orphan approval for products that are already marketed for nonorphan diseases, or multiple orphan approvals for a single product (Tribble and Lupkin 2017). Because securing an initial FDA approval is the most expensive component of new product development, the ODA's incentives are more likely to be "excessive" (i.e., beyond what's necessary to ensure commercial viability) when it comes to the approval of second, third, or fourth indications, all else being equal. These additional indication approvals thus present a risk of lavishing ODA incentives on a series of inframarginal approvals.

   The practice of securing orphan drug approval for old drugs is relatively common (Murphy, Puwanant, and Griggs 2012; Döring et al. 2016). Figures 3 and 4, for example, demonstrate that, of the 489 orphan drugs that have been approved as of year-end 2017, 68 (14%) of the approvals were secured for an orphan indication *after* initial approval for a nonorphan indication. These secondary orphan indications would be more likely to represent "gaming" (i.e., taking advantage of the ODA's benefits when they are not necessary for ensuring product viability, potentially at the expense of increased insurer and taxpayer costs) if their use for the orphan indication was widely known—or even practiced (in the form of off-label use)—in the market before the orphan approval was granted.
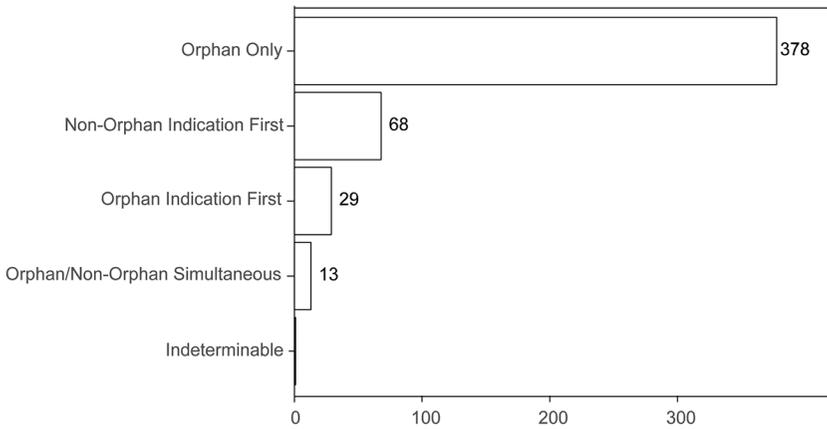
Fig. 4. Number of orphan drugs by approval sequence
Source: Drugs@FDA.
Note: Only indications approved before January 1, 2018, are included.

Consider the case of amifampridine (Firdapse, also known as 3,4-diaminopryne [3,4-DAP]), which was discovered in the 1970s and has been used for 30 years off-label to treat two rare neuromuscular diseases—congenital myasthenic syndromes and Lambert-Eaton myasthenic syndrome (LEMS). Two drug companies have recently put amifampridine through formal clinical trials for those diseases and, after securing orphan drug approval in the European Union, increased the price from $1,600 to $60,000 per year. The companies then sought approval in the United States, prompting a group of more than 50 physicians to express their concerns about the possibility of an "exorbitant pricing strategy" (Burns et al. 2016). The FDA has asked for more trials on amifampridine, but if it is approved as an orphan drug, the price for a therapeutic that has been available for decades at a relatively low cost is likely to increase dramatically. The amifampridine case appears to represent precisely the sort of "gaming" that the ODA's critics deplore.

At times, however, a subsequent approval may generate valuable evidence about a previously unknown treatment option. What might superficially appear to be gamesmanship may, in some cases, be socially beneficial. The economic question of interest is whether the extra studies needed to secure an additional indication increase social value more than the offsetting effects of higher prices and the extra government funds that are forgone as a result of the tax credit. Net social value could only increase through three (nonmutually exclusive) means. First, the

requisite clinical studies might identify new uses for already approved drugs that physicians had not yet (widely) identified through off-label use. Second, the additional clinical studies might produce valuable information on dosing and efficacy—information that may be particularly valuable for orphan indications, where the toxicity and safety profile may not be carefully recorded because the drugs target very sick patients and because the conditions, by definition, are rare. Third, the new indication could provide competitive pressure on prices for existing products that treat the same condition. Depending on the elasticity of demand for the drug, output and welfare could increase.

Multiple approvals are growing in importance as technological advances allow firms to target subtypes of existing diseases and/or indications—a practice known colloquially as "salami slicing." Most diseases have subtypes, and manufacturers can seek approval for a drug either for the broader disease or for one or more known subtypes. When some of the subtypes can be characterized as orphan diseases, the manufacturer may seek approval for one subtype after another, garnering an additional term of market exclusivity. As a result, a drug that is actually targeted at a larger population can sometimes qualify as an orphan. Physicians at Johns Hopkins University, for example, have recently documented how variations in cancer etiology enable manufacturers to secure approval for orphan indications. Because cancers can be characterized by organ (breast, brain, colon) or by their associated genetic profiles (HER2, p53, BRCA1), "almost any cancer medication can be maneuvered into an orphan disease category" (Daniel et al. 2016). Imatinib mesylate (Gleevec), for example, has received approval for seven different orphan indications. Manufacturers can thus take advantage of well-characterized disease variations in areas like oncology to extend their exclusivity period, contributing to the high prices of orphan drugs. The practice of salami slicing itself is not *necessarily* socially wasteful; rather, the value of the practice depends on whether the clinical studies necessary to secure orphan drug approval generate sufficiently valuable new information.

One suggestive test to distinguish "gaming" from socially beneficial behavior and information generation would examine a given drug's use both before and after an orphan drug approval for a secondary indication. For example, consider a world where researchers had access to complete individual-level data on the use of all products and the indication for which they were used. In such a setting, an increase in use after the approval of a new indication would suggest that the approval process provided new information to the market. In contrast,

no change in use would be more suggestive of behavior that had little social benefit—in other words, may constitute gaming.[16] In considering the change in use, it is important to also examine changes in use that may have occurred many years after the granting of the indication. Such a delay could be the result of changes to the insurance policy, such as prior authorization or formulary construction that could take some time to propagate through the system.

A case study of adalimumab (Humira, from the firm AbbVie) can help to illustrate this point, with the caveat that our claims data do not reflect all patient utilization and do not explicitly tie the purchasing of the drug with the patient's medical indication. In 2017, Humira sales were $18.4 billion, making it the best-selling drug in the United States. The product was originally approved on December 31, 2002, for an indication of rheumatoid arthritis—a condition affecting about 1% of the global population, with an estimated patient population of nearly half a million individuals in the United States (Gabriel and Michaud 2009; Helmick et al. 2008). In 2016, we estimate that 30% of sales for this drug were for its original indication, based on a large claims database, which we believe to be fairly representative of U.S. utilization.[17] Since its original approval, AbbVie has also sought and received approval for five additional nonorphan indications and four orphan indications.[18] If these additional orphan indications primarily rewarded inframarginal activity, they should have done relatively little to change use among patients with the targeted orphan diseases. If the studies necessary to receive the orphan indication yielded new information, however, we would expect changes in the product's use in those patient populations.

Figure 5, panel B, shows the percentage of overall Humira sales associated with patients with these orphan diseases. At the outset, we note that the share of overall sales for orphan indications for this product is quite low. As of 2016, despite having four orphan indications, over 90% of sales are estimated to be for nonorphan indications of the drug.

After Humira was approved for juvenile idiopathic arthritis and pediatric Crohn's disease—both of which are orphan indications—little changed in overall spending on Humira for individuals with those conditions. Nor is there evidence that use patterns changed either when the clinical trial was originally registered or when the first results were published. This flatline spending pattern is consistent with a "gaming" story: though the clinical trials were successful, they contributed little new information to the market.[19] Of particular note, use does not increase even several years after approval of the new orphan indication, suggesting that

the pattern is not merely a function of a time lag for formulary or insurance contract redesign. What explains the lack of change? Perhaps there was little postapproval diffusion of Humira to patients with the newly approved orphan indication. Or perhaps Humira was already widely used off-label for the approved indication. Off-label use may have been especially prevalent for pediatric Crohn's disease, for example, because Humira obtained approval for adult Crohn's in 2007. That's common: some orphan designations are granted for indications in small pediatric populations, even though the drug is already approved for adults and physicians may be prescribing the drug for kids. In either case, it suggests the orphan approval yielded at most only a slight social benefit.

In contrast, consider AbbVie's effort to secure orphan drug approval for Humira to treat Hidradenitis Suppurativa (HS). In the year prior, Humira spending on HS totaled only $1.75 million in the data. Immediately after the granting of orphan approval, however, there was a marked increase in the percentage of spending on Humira for individuals with this condition. In the year after receiving the orphan indication, Humira spending from patients with HS increased from approximately 1% to 3.5% of sales, with over $10 million in total sales in the data. The total percentage of Humira spending on orphan indications also rose swiftly after the drug's approval for HS. Because the R&D efforts supporting this orphan indication are associated with a sharp uptick in the use of the product, it likely represents an increase in patient welfare. That increase may or may not be large enough to justify the costs of ODA incentives. It is possible AbbVie might have sought approval for HS even without the promise of market exclusivity or tax credits. Regardless, the pattern of Humira's use for HS suggests that not all repeated orphan drug approvals reflect pure gamesmanship.

## VII.   Off-Label Prescribing of Orphan Drugs

A second type of gaming can occur if manufacturers seek orphan drug approval for a narrow indication in the expectation (a) that the drug will be extensively prescribed off-label for other, more common diseases, and/or (b) that the manufacturer will later apply for a broader, nonorphan indication. It may be easier to obtain drug approval for a product with an orphan indication than a nonorphan indication: an expedited approval pathway is available for drugs to treat unmet needs, clinical trials into orphan drugs are shorter and cheaper, and the clinical benefits for a targeted population may be easier to discern, as noted
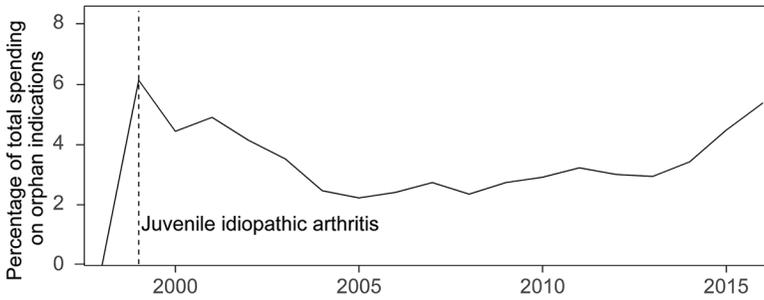
A. For Enbrel (etanercept)

Source: OLDW Pharmacy Claims.

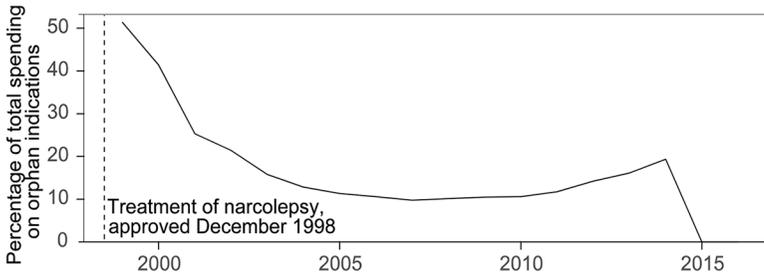Note: Singular orphan indication is labeled in the year of approval.
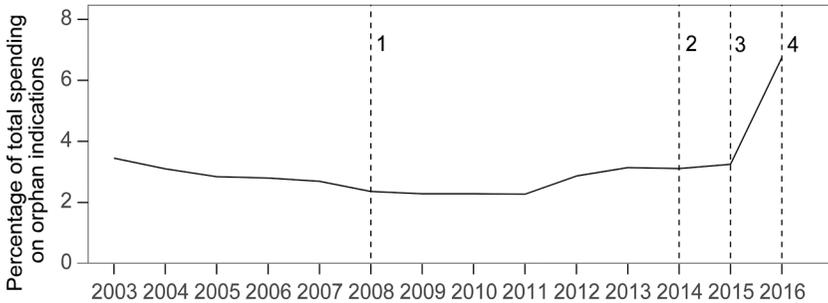
1 Juvenile idiopathic arthritis   3 Hidradentitis suppurativa
2 Pediatric Crohn's   4 Uveitis

B. For Humira (adalimumab)

Source: OLDW Pharmacy Claims.

Note: Orphan indications are labeled in the year of approval.

C. For Provigil (modafinil)

Source: OLDW Pharmacy Claims.

Note: Singular orphan indication is labeled in the year of approval. Ten or fewer pharmacy claims were filed in the year of approval.

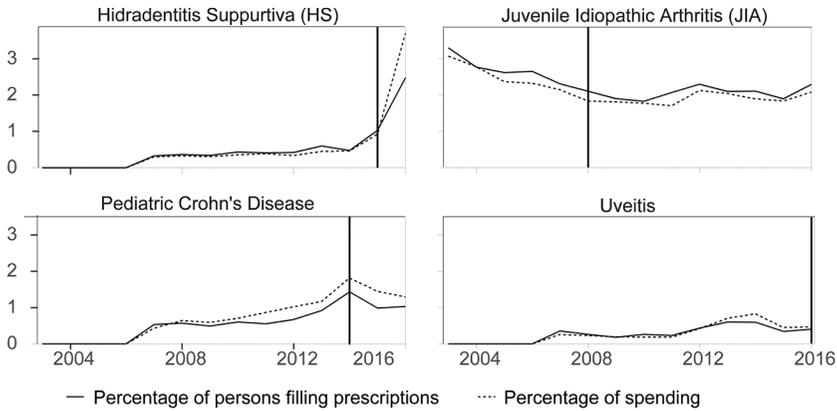**Fig. 5.** Spending on orphan indications

Fig. 6.   Spending on orphan indications for Humira by indication

Source: OLDW Pharmacy Claims.

Note: Each orphan indication is marked in the year of approval. Spending for each indication is reported as zero in years where ten or fewer persons were identified with the particular indication.

above. At the same time, however, the nonorphan uses of an orphan drug may be significant, suggesting that the drug would have come to market in the absence of ODA's incentives. A 2012 study concluded that the use of orphan drugs for nonorphan conditions is relatively common (Kesselheim et al. 2012). The lidocaine patch, for example, was originally approved to treat an orphan condition—painful hypersensitivity and chronic pain in postherpetic neuralgia—but has been prescribed for different uses 82.3% of the time.

The degree to which the initial approval for an orphan indication represents socially inefficient gaming partly depends on the manufacturer's expected returns from pursuing the initial orphan indication. If the manufacturer anticipates that the drug will be widely prescribed off-label for a nonorphan indication, orphan drug approval becomes a vehicle for expediting regulatory approval and/or reaping tax and exclusivity benefits, all while selling the drug to a much larger patient population. Orphan drug incentives could thus be misdirected to nonorphan therapeutics. In addition, firms may deliberately exploit the lower approval threshold for orphan products. Although the FDA may be comfortable allowing a potentially less safe product onto the market because it targets a small population of patients without other good treatment options, that evidence threshold may represent an unacceptable trade-off for a product that is expected to come into widespread use or may be
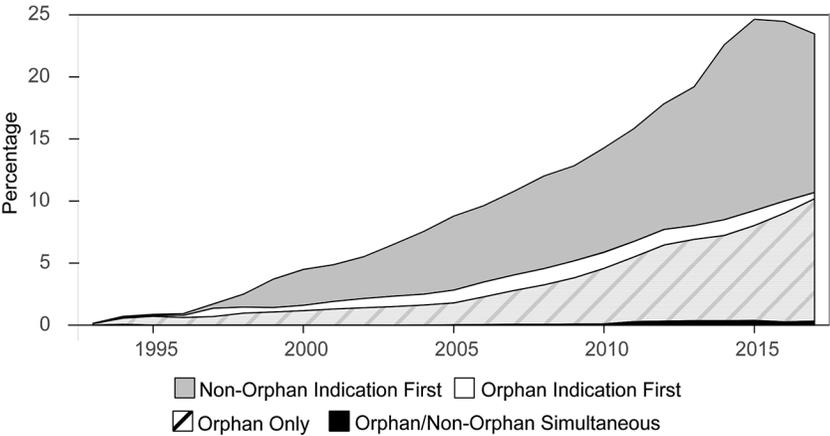
Fig. 7. Percentage of total pharmacy spending on orphan drugs by approval sequence
Source: OLDW Pharmacy Claims.

used for diseases with other established, better-understood therapies.[20] The risk of this sort of gamesmanship has likely increased over the past decade as the courts, drawing on the First Amendment, have maintained that drug manufacturers can share scientific research about off-label uses without running afoul of the federal prohibition on off-label marketing (Daniels et al. 2016).

In some cases, however, the possibility that an orphan drug might be prescribed off-label will not factor into a manufacturer's expected returns. If a drug's off-label use is serendipitously discovered, a drug manufacturer will not have "gamed" the ODA in seeking the initial orphan drug approval, even if the subsequent off-label use turns out to be extensive. In such a case, however, the profits associated with the off-label use represent a pure windfall: because they were not factored in to the initial investment decision, they have no direct incentive effects.

The identification of gamesmanship thus turns on a manufacturer's subjective expectations at the time of the initial investment. Without access to a firm's internal deliberations and confidential strategic discussions, regulators are unable to ascertain ex ante whether a drug is intended strictly for an orphan population or is expected/hoped to be sold more broadly. In many cases, the truth may lie somewhere along a spectrum. The difficulty of identifying gamesmanship ex ante, however, suggests the potential appeal of an ex post regulatory approach, in which the government recoups the monetary value of the ODA's financial incentives once a drug is sold either on- or off-label to a patient

population that exceeds the orphan drug threshold. Ex post recoupment would reduce ex ante incentives to deliberately game the system without discouraging investment in drugs that are expected to be sold only to those afflicted with rare diseases, and while maintaining a fair approach for drugs that turn out, ex post, to be widely used.

VIII.   Access to Orphan Products

The underlying impetus behind the ODA was a concern that individuals suffering from rare conditions would be left without treatment options. However, in recent years an additional concern has emerged: that the high prices of orphan drugs can lead to situations where the existence of products does not guarantee patient access. This concern was best expressed by Secretary of Health and Human Services Alex Azar who said "There's little difference for a sick patient between a miracle cure that hasn't been discovered and one that is too expensive to use."[21]

While this concern about pricing and access is fair, it is crucial to recognize that even a "first-best" orphan drug policy that targets only those products that otherwise would not be brought to market would likely have little impact on prices. Many of these products would still be patented, and the demand for the drugs would still remain strong and inelastic among their target populations. This is likely to become even more true as some treatments for extremely rare monogenic diseases like cystic fibrosis, Tay-Sachs disease, beta thalassemia, and Duchenne muscular dystrophy start to resemble "cures," as a result of advances in new drugs—including cell and gene therapies. Instead, focusing the benefits of the ODA on truly marginal products would likely decrease the number of products that receive orphan drug benefits. This may lower prices for the inframarginal products that currently receive ODA protection, and could open up the possibility of earlier generic competition in a contestable market.

If policymakers are concerned about the high prices of orphan drugs, either in addition to or simply instead of the existence of these products, payers must be given the freedom to more carefully consider the value of the drugs that they purchase. Almost by definition, orphan drugs represent the only product in a therapeutic category and thus are likely to be included on a formulary even if they provide relatively little value. Forcing such a drug into a bundle with a large number of other value-creating products can allow manufacturers to charge high prices, sometimes prices that exceed the value of the product (Besanko et al.

2016). Where an orphan drug is not cost effective—when it yields only incremental health improvements but has an enormous price tag—lower prices will only come if payers are empowered to say "no." Some governments have taken steps in that direction. Sweden, for example, has declined to pay for about half of newly approved orphan drugs (Garau and Mestre-Ferrandiz 2009). If a critical mass of developed nations followed Sweden's lead, drug manufacturers would come under considerable pressure to cut their prices or to focus on the commercialization of higher-value therapeutics.

IX. Discussion

An efficient policy would target incentives toward those firms and products that create meaningful improvements for small patient populations and are not otherwise economically viable investments. In developing such regulations, policymakers must confront three broad questions: (1) which products should receive assistance, (2) whether all products should receive the same benefit, and (3) what incentives the government should provide to firms developing those products. We will discuss the economics underlying each of these decisions in turn.

We first consider the question of which products should receive assistance. As discussed above, a "first-best" orphan policy would target only those products that otherwise would not be brought to market. For many reasons, this is quite hard to ascertain ex ante, and as a result, it appears that many firms currently receive economic benefits for investing in inframarginal products that would otherwise be developed.

This situation is a function, in part, of the inherent inflexibility of tying orphan drug approval to a fixed threshold of disease prevalence. By definition, any fixed threshold cannot adjust to changing market conditions. As markets evolve—whether due to changing costs of product development or the potential revenues from a successful investment—the optimal threshold associated with economic viability will shift. If development costs fall and revenues increase, for example, an increasing share of (now) inframarginal products will be eligible for ODA benefits. The evidence suggests this has already occurred: prices have increased steadily and dramatically for orphan drugs over the past 35 years, with no countervailing change in the prevalence threshold. And the evidence suggests it will continue occurring in particular sectors of the pharmaceutical market, where the increased use of biomarkers is both decreasing the costs of some clinical trials (Chandra, Garthwaite,

and Stern 2017) and may enable more effective (and more lucrative) indication-based pricing (Chandra and Garthwaite 2017).

Related to the question of which products should receive benefits is a question of whether all products receiving orphan approvals should receive the *same benefits*. The current ODA provides a single benefit structure enjoyed by all firms successfully receiving a designation and subsequent approval, regardless of the underlying economics of the product's potential market. This creates a problem similar to providing incentives to inframarginal products. A uniform benefit means that, by definition, some products that are actually marginal (in that they would not be brought to market without some level of assistance) still receive benefits that exceed what would be required to incentivize the firm to invest in the product. In addition, products requiring larger amounts of assistance in order to be economically viable may never be brought to market.

The ODA's uniform benefit structure implies that it will often confer excessive benefits when firms seek orphan approvals for additional indications for existing products, particularly when those products lack patent protections and are in widespread use. For these indications, early-stage trials have already demonstrated safety, and thus development costs are likely to be much lower than for a totally new product. Similarly, benefits may be excessive for those firms that anticipate a large volume of off-label sales for a drug that comes to market as an orphan. That is particularly true given that the lower threshold for clinical trials for orphan products likely results in lower development costs for these products. On the other side of the ledger, firms receive fixed benefits whether or not a drug candidate is likely to face meaningful generic competition. For products in markets where manufacturers expect little generic competition (i.e., those that more closely resemble natural monopolies), market exclusivity offers little value and therefore provides few *additional* incentives for commercialization. In this situation, market exclusivity cannot correct a perceived investment shortfall in orphan drugs.

Both the concerns about rewarding inframarginal products and providing an inappropriate level of assistance to marginal products could be addressed if the fixed, numerical prevalence threshold were abandoned. The ODA could be amended to return it to its original form, one that referenced explicitly the economic viability of a product that is developed to treat a disease afflicting a small patient population. Policymakers could then target incentives to novel drugs or to novel

uses for existing drugs. In many instances, for example, firms receive the benefits of the ODA for a new indication for a product that is already widely available. As the Humira case study suggests, new indications can sometimes create value in the form of increased use. In other cases, however, new indications appear to simply codify an existing off-label use, which provides fewer welfare benefits. Depending on whether a new indication demonstrates a genuinely novel use for an existing drug, orphan drug approval will have different effects on welfare and will likely present a different value proposition for firms. An ideal policy would acknowledge those differences and adjust incentives accordingly.

Shifting to a standard of economic viability, however, is easier said than done. At a minimum, identifying drug candidates that truly need additional R&D support would require providing regulators with new legal authority. In addition, regulators would require meaningful new resources and expertise to adequately shoulder these new responsibilities. For example, understanding the potential value of a new use might require regulators to systematically monitor off-label use of existing products. They might also need to employ sophisticated economic models, supplemented with data from private insurers, to estimate a drug's expected market value and determine whether manufacturers are likely to require additional incentives for particular classes of drugs.

These potential costs highlight the appeal of a bright-line rule to qualify for orphan drug status. Such a rule is intrinsically easy to understand and administer. The appeal of extending uniform benefits to all drugs with an orphan drug approval follows similar logic: it yields certainty for manufacturers and regulators alike. In both cases, simplicity reduces decision costs and mitigates certain risks of gamesmanship and regulatory capture. Significantly, too, FDA regulators currently lack the resources and the information necessary to evaluate the financial viability of drug candidates and the social value associated with their approval ex ante. An easy-to-administer rule relieves the agency of that responsibility.

It is not clear, however, that the benefits associated with a rule-bound approach outweigh its costs—especially as the costs of that rule-bound approach increase over time. It certainly is unlikely that any implicit calculations supporting the policy choices made in 1984 remain valid in the pharmaceutical market that has emerged over subsequent decades. In addition, we should note that the tools for estimating the financial viability of potential new therapies do exist and the FDA could employ

them to better target incentives for drug development. While implementation difficulties should be considered, they should not stand as an insurmountable obstacle to more efficient policy.

Setting aside which drugs should receive incentives, policymakers should also consider the nature of those incentives. Currently, the ODA provides two types of incentives: a period of market exclusivity and an R&D tax credit. Both are intended to increase the expected profits of an investment in drug development by both lowering the costs and increasing the revenues associated with the commercialization process. The funding sources of these two incentives are distinct, however, and their economic impacts differ meaningfully.

The tax credit is funded from general tax revenue and therefore has a relatively broad base of financial support. Thus, inefficiency arises from the general deadweight loss of raising government funds and the opportunity cost of how those funds could be otherwise spent. In contrast, the period of market exclusivity results in a protracted period of higher drug prices. In a world with no cost sharing, those prices would spur higher insurance premiums across the entire risk pool. Higher premiums would in turn distort the purchase decision for insurance; the resulting welfare losses would fall most acutely on the privately insured. Those cost burdens are compounded to the extent that insurers employ differential cost sharing for orphan and other specialty products. In that case, the benefits of orphan products would be financed, in part, through an effective tax on individuals with orphan conditions. That tax partly unwinds the insurance product for those individuals, resulting in an inefficiently low consumption of drugs and an inadequate level of risk protection.

These differential funding sources imply that in some cases tax credits may be a superior incentive mechanism relative to extended market exclusivity. The case for tax credits becomes stronger because they can be *clawed back* by regulators in the event that the product is more successful than expected at the time of its orphan drug application. Exclusivity periods can also be terminated—EU law, for example, allows a reduction of the exclusivity period to six years when a drug is deemed sufficiently profitable, though that authority has not been exercised. Terminating an exclusivity period, however, may not immediately induce competition, even in rivalrous markets. Generic manufacturers may be uncertain about the date that the exclusivity period will lapse, increasing the uncertainty associated with the development of a competitor product. If generics' ability to time entry into the market is compro-

mised, manufacturers could maintain de facto exclusivity for some period after the de jure period ends—a feature that speaks for the ongoing attractiveness of gaming, even in a world where exclusivity can be revoked.

Terminating tax credits, in contrast, would not have a similar effect on market dynamics. Under a system where firms were required to document economic viability, a modified ODA could empower the government to automatically claw back the value of the credit if and when a firm's revenues exceed those documented in the orphan drug application. Only windfall profits would be recouped, which (properly administered) should not affect a firm's ex ante investment choices. In addition, such a system has already been shown to be administrable: in Japan, for example, manufacturers must repay R&D subsidies for drugs with annual sales that exceed 100 million yen (Wellman-Labadie and Zhou 2010). Tax credits are not panaceas: firms may be able to game such a tax credit by allocating fixed costs that were not truly related to the development of an orphan product. They do, however, have distinct advantages over fixed periods of market exclusivity.

Regardless, meaningfully changing ODA incentives would be especially attractive if the definition of an orphan drug shifted away from disease prevalence and toward financial viability. If eligibility for orphan drug status or the size of R&D incentives hinged on an ex ante assessment of economic viability, firms would, at the margin, be tempted to game the system, either by overstating costs or understating potential revenues. Because regulators would have a difficult time preventing such gamesmanship, terminating incentives once a manufacturer has recouped its risk-adjusted R&D investment might be a more constructive approach.

Ultimately, adapting the ODA to the twenty-first century will demand a careful evaluation of a complex set of questions. Which products should be targeted? What incentives should be provided? What regulatory resources can be mustered? In an ideal world, affording greater flexibility to regulators could allay many of the economic concerns associated with the current regime. In a non-ideal world, however, it is an open question whether regulators have (or will be given) the capacity, legal authority, and resources to develop and fairly administer a better-calibrated orphan drug policy. At a minimum, policy approaches that allow the government to direct incentives to the development of orphan drugs that would otherwise not be economically viable hold substantial promise.

Endnotes

1. In the United States, every new chemical entity approved by the FDA receives five years of market exclusivity. A new chemical entity that is approved as an orphan product, however, also receives a seven-year period of orphan drug exclusivity, which runs concurrently with (and thus extends two years beyond) the five years of exclusivity for new chemical entities. A previously approved product can receive multiple orphan indications, with a separate seven years of regulatory exclusivity for each new indication.

2. See 21 C.F.R. §§316.20 & 316.21. A manufacturer can also seek an orphan designation for conditions that target more than 200,000 patients, but only if it demonstrates that "no reasonable expectation that costs of research and development of the drug for the disease or condition can be recovered by sales of the drug in the U.S."

3. Pub. L. No. 115-97, 13401(a).

4. Report on Tax Expenditures for Fiscal Year 2019. https://www.treasury.gov/resource -center/tax-policy/Documents/Tax-Expenditures-FY2019.pdf.

5. The general equilibrium welfare implications of this are unclear, as the existence of market exclusivity increases the availability of products.

6. Chimeric antigen receptor, or CAR T-cell therapy, is a relatively new form of immunotherapy that uses specially altered T cells to more specifically target cancer cells (http://www.dana-farber.org/cellular-therapies-program/car-t-cell-therapy/).

7. This discussion may make it seem as if biomarkers increase the ability to price discriminate only where a drug has both orphan and nonorphan uses. But even for drugs with solely orphan applications, a biomarker that better predicts benefit (e.g., by identifying a particularly rare genetic defect) will facilitate the drug being deployed in those patients with the greatest benefit; this, in turn, increases the price that can be charged.

8. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm.

9. https://www.arthritis.org/about-arthritis/types/rheumatoid-arthritis/what-is -rheumatoid-arthritis.php.

10. This report is available at: https://www.iqvia.com/institute/reports/orphan-drugs -in-the-united-states.

11. Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98–417, 21 U.S.C. § 355(j) (1984).

12. The FDA's Biomarkers, EndpointS and other Tools (BEST) glossary defines a biomarker as a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions (https://www.ncbi.nlm.nih.gov/books/NBK326791).

13. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopment ToolsQualificationProgram/BiomarkerQualificationProgram/default.htm.

14. The two categories overlap to some extent: for example, certain cystic fibrosis transmembrane conductance regulator mutations can be used as both diagnostic and predictive biomarkers to select patients for therapies or clinical trials.

15. However, other costs associated with clinical research, such as patient recruitment, may go up in this setting.

16. For completeness, it is important to note that this would also be consistent with a simple error by a firm that expected an increase in utilization from the new indication, but was wrong. It would also be consistent with limited or absent coverage by payers for a new orphan drug—even "on-label."

17. While we lack complete insight into the rebate structure, this is a smaller concern when examining the distribution of expenditures across indications within a product because rebates are not currently tied to particular indications.

18. Humira approval history (orphan indications in bold):

Date	Indication	Date	Indication
12/31/02	Rheumatoid arthritis	2/21/08	**Juvenile idiopathic arthritis**
10/3/05	Psoriatic arthritis	9/28/12	Ulcerative colitis
7/28/06	Ankylosing spondylitis	9/23/14	**Pediatric Crohn's disease**
2/27/07	Adult Crohn's disease	9/9/15	**Hidradentitis Suppurtiva (HS)**
1/18/08	Plaque psoriasis	6/30/16	**Uveitis**

19. As noted above, this conclusion requires that the drug has broad coverage among patients (e.g., without requiring preauthorization).

20. This source of inefficiency should not be confused with applying "orphan drug" prices to a broader population. To the extent that the manufacturer is a rational profit-maximizing firm, it will set a price that would cause a payer to allow the broader population access to the product. This is particularly true given that a payer can relatively easily implement utilization management techniques to limit access to a product for off-label indications.

21. http://thehill.com/policy/healthcare/385805-hhs-secretary-trump-drug-pricing-plan-will-go-much-further-than-budget.

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