PharmacoEconomics (2020) 38:1115–1121
https://doi.org/10.1007/s40273-020-00934-2

ORIGINAL RESEARCH ARTICLE

Market Exclusivity for Drugs with Multiple Orphan Approvals (1983–2017) and Associated Budget Impact in the US

William V. Padula[1,2] · Sonal Parasrampuria[3] · Mariana P. Socal[3] · Rena M. Conti[4] · Gerard F. Anderson[3]

Published online: 12 June 2020

Abstract

Objectives The *Orphan Drug Act* extends exclusivity of branded drugs by 7 years for each rare disease approval. By extending market exclusivity, manufacturers can forestall generic competition. We determined the prevalence of drugs with multiple orphan approvals, the duration for which manufacturers are able to maintain exclusivity using this mechanism, and the budget impact of these additional exclusivity periods on US spending on orphan drugs.

Methods We analyzed a retrospective cohort of US orphan drug approvals filed between 1983 and 2017. Drug costs throughout this time period were measured using IQVIA claims data. We estimated additional years of exclusivity per drug per orphan approval using mixed-effects negative binomial regression. The budget impact analyzed potential cost-savings for exclusivity periods greater than 7 years after the initial orphan approval based on potential price reductions from the introduction of biosimilar/generic competition.

Results A total of 432 branded drugs were approved for 615 orphan indications, of which 108 had multiple indications. Market exclusivity, beyond the initial 7 years, increased by 4.7 years with two orphan approvals, and there were 3.1-, 2.7-, and 2.9-year extensions for three, four, and five approvals, respectively ($p < 0.05$). Drugs with five approvals averaged 13.4 additional years of exclusivity. Sixteen drugs had exclusivity periods extending at least 1 decade beyond the original exclusivity period. The potential budget impact of additional exclusivity was estimated at US$591 billion for 7 years following the end of the first approval.

Conclusions Multiple blockbuster drugs have received exclusivity of > 10 years through the *Orphan Drug Act*, thereby delaying rare disease cohorts' access to generic/biosimilar equivalents.

1 Introduction

Since passage of the *Orphan Drug Act* in 1983 until May 23, 2017, there were over 400 drugs approved to treat rare diseases in the USA [1]. The US Food and Drug Administration (FDA) approves drugs filed for orphan status if the disease has < 200,000 prevalent cases [2]. Under current law, there are no limits on the number of orphan approvals a company can seek if the drug is safe and efficacious in a different patient population [2].

Manufacturers receive 7 additional years of market exclusivity for the approved rare disease indication from the time of approval in addition to 5 years of initial market exclusivity after the FDA approves a new drug, though these timeframes can overlap [1]. This exclusivity means that no other manufacturer can obtain FDA approval for a generic or biosimilar compound to treat the same indication. Manufacturers also receive a tax credit on the cost of clinical trials related to the rare disease, which was reduced from 50 to 25% in the 2017

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40273-020-00934-2) contains supplementary material, which is available to authorized users.

✉ William V. Padula
padula@healthpolicy.usc.edu

1 Department of Pharmaceutical and Health Economics, School of Pharmacy, USC Schaeffer Center, University of Southern California, 635 Downey Way, Los Angeles, CA 90089, USA

2 Leonard D. Schaeffer Center for Health Policy and Economics, University of Southern California, Los Angeles, CA, USA

3 Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

4 Institute for Health System Innovation and Policy, Boston University Questrom School of Business, Boston, MA, USA

Key Points for Decision Makers

The *Orphan Drug Act* of 1983 has been instrumental in spurring innovation of over 400 drugs in the USA indicated for rare diseases (< 200,000 patients). The act provides drugs with 7 additional years of market exclusivity for the rare disease indication, as well as a 25% tax credit on clinical trial costs associated with the orphan approval.

Access to these drugs is a concern because extended periods of exclusivity among branded drugs that retain orphan indications lead to higher costs. Because there is no limit on the number of orphan indications a drug can obtain, certain drug manufacturers may be timing the filing of orphan designations to maximize the duration of exclusivity.

Our study identified that 16 drugs, 4% of new drug approvals since 2000, obtained three or more orphan approvals, maintaining exclusive rights to certain rare disease indications for an additional 14 years. Some of these drugs retained market exclusivity as they reached their 20th year on the market because of orphan indications. This could have a potential budget impact of US$591 billion due to a lack of available generic/biosimilar substitution.

US *Tax Cuts and Jobs Act* [1, 3]. The *Orphan Drug Act* has stimulated research and development in orphan diseases, and for this reason, Reaves has noted its considerable success in achieving its objective [4].

However, there is growing concern that the unlimited nature of market exclusivity provisions proffered by the *Orphan Drug Act* may reduce the availability of affordable drugs to American patients and payers by forestalling generic competition. Currently, treatments for orphan drugs can cost more than US$30,000 per course of treatment (i.e., the duration of therapy inside of 1 year). This US$30,000 mark is significant because it approximates the threshold for the top 10% of the most expensive drug treatment courses in the USA, and coincides with state law used to establish the Maryland Prescription Drug Affordability Board's cutoff for high-priced drugs above which patients could have accessibility issues [5]. Others have also documented a lack of available generics and biosimilars for orphan diseases where an orphan indication has previously been approved, even if a particular drug no longer holds exclusivity for an indication, including types of cancer, immunology, rheumatology, and other diseases [6]. While the additional market exclusivity period only applies to the new patient population, pharmacies could be reluctant to stock both the generic and branded versions of the same drug for several reasons, including safety concerns; ease of administration of certain branded drugs which have patented delivery mechanisms, as opposed to alternative generics or biosimilars which may present less convenient delivery mechanisms for patients or their providers to follow (e.g., injection vs. infusion); and the fact some payers will not pay for the generic drug when a subset of the population is still taking drugs that also have indications related to orphan exclusivity.

Therefore, there are several important, and to date, unanswered questions: (1) how often do companies use provisions of the *Orphan Drug Act* to extend the market exclusivity period? (2) Are there characteristics of drugs that have been able to delay entry of generic drugs the longest? And (3) are provisions of the act financially impacting the US drug market to the extent that a lack of generics and biosimilar availability means prolonged periods of more expensive drugs for particular indications and, therefore, reduced accessibility? We explored these questions by studying patterns of exclusivity periods in orphan drugs in order to establish a potential budget impact for sustainment of the current version of the act. The premise is whether multiple filings for orphan approvals were in fact clustered, "stacked," to extend exclusivity periods.

2 Methods

2.1 Approach

We used data from the FDA Orphan Drug Designations and Approvals query to extract all orphan drug designations and approvals from January 1, 1983 through May 23, 2017 [7]. "Exclusivity" refers to exclusive marketing rights granted by the FDA upon orphan drug approval [8]. For each drug, we used the designation and approval dates to calculate the length of time from initial approval date to the end of the market exclusivity period.

To evaluate whether sequential indications increased market exclusivity time, we analyzed the effect of each approval on market exclusivity. We used a mixed-effects negative binomial regression to examine the additional duration of exclusivity a drug achieved with each additional orphan drug approval, controlling for *time* fixed effects. We performed sensitivity analysis using fixed and random effects and selected the final version of the model based on significant reductions in the log-likelihood ratio. We also tested multiple correlation structures to ensure improved model fit (i.e., independent, unstructured, exchangeable, and autoregressive). In the final model, approximately 18.8% of the standard deviation was explained (R-squared = 0.34).

2.2 Economic Evaluation

We modeled the budget impact of the *Orphan Drug Act* on US drug spending beyond the initial 7 years of exclusivity associated with branded drugs that had four or more orphan approvals. Pharmaceutical claims data were licensed from IQVIA (Durham, NC) in order to obtain information on total US spending for drugs taken by patients with rare disease diagnoses. Total spending in standardized dollars for claims filed in IQVIA were obtained by year between 2004 and 2016. Estimated drug prices per course of treatment per year were then derived in terms of the cost per patient by dividing the total amount spent on each drug indication by the number of patients diagnosed with the specified disease in the IQVIA data. The budget impact analysis applied the estimated cost per patient for an orphan indication according to IQVIA data corresponding to the year of observation.

To calculate total expenditures, the estimated cost per patient was multiplied by the total number of patients in the USA estimated to have a particular orphan diagnosis. We obtained information on the total estimated number of patients in each rare disease cohort filed with the FDA. These data were requested from the FDA through the *Freedom of Information Act*.

The model determined the budget impact based on the variability in cost per patient over time throughout exclusivity, up until the seventh year. After the seventh year, the price of a small molecule was modeled to fall between 60 and 90% with the availability of generic alternatives based on previous estimates by Conti and Berndt, or the price of a biologic could drop by 10–30% with the introduction of a biosimilar [6]. Biologics are less likely to observe the same magnitude of price drop since biosimilars require greater investment in research and development to reach the market [9, 10]. We limited the budget analysis to those drugs most likely to have price drops, due to their popularity as "blockbuster" drugs with market demand for lower-priced, nonbranded alternatives. The total budget impact was estimated as the average percentage decrease in price for biologics, an expected value of 20%, and small molecules, an expected value of 75%. Credible intervals (CIs) for the budget impact were also calculated for price drops ranging from a lower limit of 10% and 60% to an upper limit of 30% and 90% for biologics and small molecules, respectively.

3 Results

3.1 The Number of Orphan Approvals Keeps Increasing

From passage of the law in 1983 through May 23, 2017, there were 615 approved orphan indications involving 432 unique drugs (Fig. 1). When the *Orphan Drug Act* was introduced in 1983, the number of orphan drug approvals increased slowly, at a rate of approximately 2%; however, over time, the rate of approvals has increased exponentially to exceed 66% after 1990 (Fig. 1).

On average, drugs had 1.47 approvals with an extended market exclusivity period of 1.6 years. However, there were a significant number of outliers, 108 drugs, which made up 25% of orphan drugs. These 108 drugs had two or more orphan approvals, presenting an opportunity for manufacturers to time the approval of their additional orphan disease cohort indications to extend market exclusivity beyond the initial 7 years.

This is supported by empirical evidence; drugs with additional orphan approvals increased the market exclusivity period. Based on the statistical model, we determined that drugs with a second orphan approval were associated with an average increase of 4.7 years in market exclusivity after the initial approval (Table 1). The third approval resulted in an average of 3.1 additional years of market exclusivity, the fourth 2.7 additional years, and the fifth 2.9 additional years of exclusivity on average ($p < 0.05$). When all the approvals are combined, orphan drugs with five approvals received an average of 13.4 additional years of market exclusivity, nearly tripling the initial market exclusivity period. There are relatively few approvals after the fifth approval, and the results are not statistically significant.

3.2 Drugs with the Longest Market Exclusivity Periods Benefited from Timing Decisions

Of all drugs approved for orphan indications, 13 drugs had a market exclusivity period with at least an additional decade

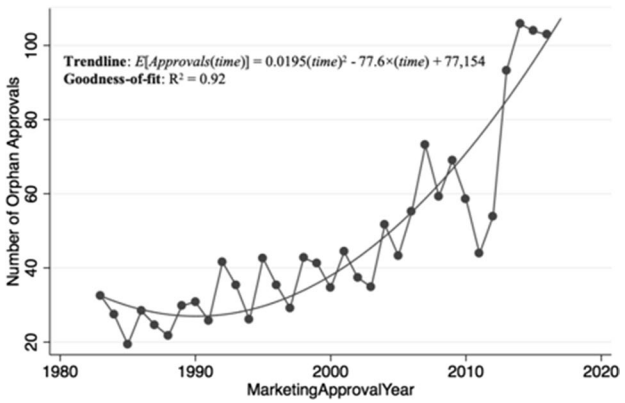

Fig. 1 US FDA Orphan Drug Approvals between 1983 and 2017. Over 34 years, there have been 615 approved orphan indications for 432 registered pharmaceuticals. This represents a rate of 1.42 (SD = 1.01) orphan approvals per drug and 1.64 years (SD = 4.37) of market exclusivity extension for each approval. Source: FDA Orphan Drug Designations and Approvals from January 1, 1983 through May 23, 2017. *FDA* Food and Drug Administration, *SD* standard deviation

beyond the original period of exclusivity (Fig. 2). Seven of those drugs achieved market exclusivity for 2 decades or more: adalimumab, bevacizumab, bortezomib, coagulation factor VIIA, filgrastim, imatinib, and lenalidomide. These drugs had five or more approved orphan indications. However, most of these approvals occurring in the second decade after initial orphan approval were initially filed in the first 10 years after orphan designation. Thus, a combination of delays in the conduct of research and FDA filings may have led to these drugs receiving very long exclusivity periods.

3.3 Budget Impact

Based on these findings, there were seven biologics and five small molecules that had multiple orphan approvals that extended exclusivity beyond the seventh year following an initial orphan approval. Using our criteria for the budget impact analysis (see the electronic supplementary material), the potential increase in spending across all observed drugs and orphan indications based on claims data was US$591.1 billion (CI US$392.6 billion to US$789.6 billion) (Table 2). If the analysis excluded botulinum toxin type A and filgrastim, since both have biosimilars, the budget impact remains US$561.0 billion (CI US$377.5 billion to US$744.5 billion). This budget impact represents an approximation of the money spent on branded versions of these drugs following the first 7 years of orphan exclusivity. Different drugs had different price reductions following generic entry.

Table 1 Negative binomial regression model analyzing the longitudinal (i.e., *time*-dependent) fixed-effects analysis of the incremental time period for each additional Orphan Drug Approval filing between 1983 and 2017

Variable	Approvals		
	Number of drugs	Proportion of orphan drugs (%)	Regression coefficients (SE)
1st filing	432	Reference	Reference
2nd filing	108	25	4.43** (0.27)
3rd filing	34	8	3.07** (0.47)
4th filing	17	4	2.68** (0.66)
5th filing	10	2	2.94** (0.78)
6th filing	4	1	0.47 (1.22)
7th filing	4	1	1.99 (1.22)
8th filing	3	1	0.60 (1.40)
9th filing	2	0.5	1.91 (1.72)
Time	–		0.01 (0.01)
R-squared			0.34

SE standard error

$^{**}p < 0.01$

4 Discussion

When the *Orphan Drug Act* was passed in 1983, there were few biologics and drugs that focused on rare diseases. The legislation fostered research and development in rare diseases, something that has benefited many individuals. Despite the benefits from having additional testing of the drugs in new populations, there is a tension between the benefits to society of the second and third orphan approval and the excessive cost of extending the exclusivity period, which in turn limits generic/biosimilar availability for particular indications. Policymakers may not have anticipated the numerous times a drug company would apply for orphan status or that they would stack them in a way that significantly prolonged the market exclusivity period.

The extension of market exclusivity reduces the possibility of generic competition in the future, the benefit of which is that it can reduce prices of specialty drugs by up to 90% [6]. Since the price of many orphan drugs can exceed US$50,000, maintaining orphan status can significantly restrict access for many patients given the cost sharing tiers many insurers impose on high-priced orphan drugs. Patient

Drug	Year																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	>20
Adalimumab (AbbVie, Inc.)	A,B	C		**1**						D, **2,3**	E,**4**,-1	**5**					-2,-3	-4	-5		
Bevacizumab (Genentech, Inc.)	A			B,C,D			**1,2**	E,F,G,H				**3**	**4,5**		**6,7,8**,-1,-2					-3,-4,-5	-6,-7,-8
Bortezomib (Millenium Pharamaceuticals, Inc.)	A,B,C,**1**		**2**	**3**		**4**		-1		D,E,-2	-3	**5**	-4						-5		
Botulinum Toxin Type A (Allergan, Inc.)	A,B		C			**1,2**							-1,-2				**3**				-3
Canakinumab (Novartis Pharmaceuticals Corporations)	A	B	**1**			C	D,E,2			**3,4,5**,-1				-2			-3,-4,-5				
Coagulation Factor VIIA (Novo Nordisk, Inc.)	A											**1**					B,C,D,E,F,G	**2,3,4**	**5,6**,-1		**7**,-2,-3,-4,-5,-6,-7
Everolimus (Novartis Pharmaceuticals Corporations)	A,B	C,D	**1**	**2**	**3**				**4**	-1	-2	-3				-4					
Filgrastim (Amgen, Inc.)	A,B				**1,2**	C,**3**	D		**4**			-1,-2	-3			-4					E,**5**,-5
Ibrutinib (Pharmacyclics, Inc.)	A,B,C,D	E,F,**1**	**2,3**	G,H,**4**	**1,5,6**	**7,8,9**			-1	-2,-3	-4	-5,-6	-7,-8,-9								
Imatinib Mesylate (Novartis Pharmaceuticals Corporations)	A,B,C,**1**	**2**			D,E,F,G,H,I	**3,4,5,6,7**		**8**,-1	-2				**9**,-3,-4,-5,-6,-7		-8					-9	
Lenalidomide (Celgene Corporation)	A,B,C			D	**1**	**2**			E			-1	**3**,-2		**4**		**5**			-3	-4,-5
Mitoxantrone (Serano, Inc.)	A,**1**			B,C	**2,3**			-1				-2,-3									
Ofatumumab (Novartis Pharmaceuticals Corporations)	A,B,C,D,**1**					**2**		**3,4**,-1					-2		-3,-4						

Legend: Letters (e.g. A, B, C) indicate new designations; Bold positive numbers (e.g. **1, 2, 3**) indicate approvals; Negative numbers (e.g. -1, -2, -3) indicate the end of exclusivity for the corresponding approval.
Gray shaded cells represent the period when a drug was on the market with at least one exclusive indication.

Fig. 2 The 13 orphan drugs (and their manufacturers) with more than 4 approvals between 1983 and 2017 that result in exclusivity extensions beyond 1 decade. Manufacturer names are in parentheses

Table 2 The US societal budget impact [cost (credible interval)] of maintaining branded prices on drugs with orphan indications beyond the 7th year of exclusivity

	Budget impact of biologics[a] (US$ billions) inclusive of all biologics	Budget impact of small molecules[b] (US$ billions)	Budget impact of biologics[a] (US$ billions) exclusive of biologics with 2 + biosimilars	Budget impact of small molecules[b] (US$ billions)
	$267.6 ($133.8–$401.4)	**$323.5** ($258.8–$388.1)	**$237.6** ($118.9–$356.4)	**$323.5** ($258.8–388.1)
Estimated total budget impact	**$591.1** ($392.6–$789.6)		**$561.0** ($377.5–$744.5)	

Our analysis explored 7 biologics delivered intravenously and 5 small molecules delivered orally. The budget impact was estimated based on price drops of 20% (range 10–30%) on average after the 7th year for biologics and 75% (range 60–90%) on average for small molecules. These data are based on an analysis of IQVIA drug claims (2004–2016) and FDA Orphan Drug Designations and Approvals (January 1, 1983 and May 23, 2017). Bolded numbers indicated expected values

FDA Food and Drug Administration

[a]There were 7 biologics with orphan approvals beyond the 7th year of orphan drug exclusivity: adalimumab, bevacizumab, botulinum toxin type A, canakinumab, coagulation factor VIIA, filgrastim, and ofatumumab. Botulinum toxin type A and filgrastim were excluded in the second calculation since both biologics have 2 + biosimilars

[b]There were 5 small molecules with orphan approvals beyond the 7th year of orphan drug exclusivity: bortezomib, everolimus, ibrutinib, imatinib mesylate, and lenalidomide

assistance programs can improve access, but they distort the market by eliminating cost sharing [11].

Additionally, stacking multiple orphan drug approvals may result in total orphan populations of more than 200,000 individuals. This raises the question of whether a drug used to treat over 200,000 individuals remains an "orphan drug." While this study did not measure the number of individuals included in each of the indications, there are a number of drugs where this has occurred. Among the list of drugs in Fig. 2, the total number of patients treated with adalimumab, bevacizumab, bortezomib, ibrutinib, lenalidomide, and ofatumumab in the US based on approved orphan indications exceeds 200,000 patients in total. These observations give rise to the argument that while these drugs may be treating patients with rare diseases, they are not orphan drugs since they are commonplace in the US healthcare sector and profitable to produce without government assistance.

Drug manufacturers need to be appropriately incentivized and remunerated for entering the orphan drug market. It is very expensive to do the research and development to create a new drug. However, the cost of conducting a clinical trial on a new population with an existing FDA-approved drug is much less [12]. A drug that was initially developed for a rare disease cohort received a tax credit and 7 years of market exclusivity to ensure that the branded price would allow them sufficient profit to reinvest in innovation. However, multiple indications and additional exclusivity can allow manufacturers to generate additional profits without considerable additional expense. This is especially a concern if a drug is not initially developed to treat a rare disease, but is later used to treat a much larger population. Nine of the drugs (69%) in Fig. 2 were introduced on the market for common diseases first before receiving an orphan approval several years into their availability.

Surprisingly, there is anecdotal evidence that having an orphan status for even one use can mean that many pharmacies, hospitals, and nursing homes may not stock the generic version, because of a concern that it will be administered to the patient with a disease that still has orphan status, and thus not be covered by insurance. This is a practical reason why getting orphan status can be significant even if the drug is a “blockbuster.”

4.1 Limitations

First, we were unable to examine drugs that did not apply for orphan drug designations. Second, we did not categorize orphan drugs in regard to whether they were originally developed for the orphan market or whether they were developed for the mass market first and sought orphan designations afterwards. The adverse consequences of orphan designations are especially problematic if the drug was first on the mass market and later applied for orphan status, because while the mass market use has become generic, the orphan status could cause many hospitals, nursing homes, and pharmacies to only stock the branded drug. Third, we did not examine the impact of additional orphan designations on the number of users of the drug. Clarifying the changes in the scope and utilization of a drug brought upon by additional orphan designations—number of users, prescription practices, and reimbursement policies implemented by payers—could help identify the extent to which the original intents of the *Orphan Drug Act* have been distorted by stacking of designations.

Fourth, we did not examine the association between long-term market exclusivity and patent life of a drug, specific to adult or pediatric indications. Sarpatwari and colleagues have found that significant proportions of orphan drugs have market exclusivity periods outlasting the last expiring patent, which suggests that the exclusivity guarantees within the act may provide the stronger of the two incentives [13]. Grabowski and colleagues note that some patents expire during clinical trials, but that most have protections that last about 13 years before generic competition normally arises [14]. Thorat and colleagues also note that pediatric rare diseases have different benefits from the act than adult populations, and these benefits are also linked to patent laws [15]. Furthermore, we are unable to test how manufacturers' would alter their behavior were the act to be revised so that the number of patent filings was fewer. In other words, makers of orphan drugs may be willing to pursue those drugs not only because of the first filing's patent protection, but also because there is a chance to obtain additional years of market protection. Given the collinearity between patent protection and exclusivity, a mixed-methods study design to better understand manufacturers' aims with respect to patient protection would be interesting future research.

Fifth, the price-drop modeled in the budget impact analysis of between 60 and 90% is assumed based on the analysis of Conti and Berndt applied to cancer treatments [6]. Many of the cancer treatments explored in their analysis overlap with this analysis, such as imatinib. However, their analysis is not comprehensive of drugs in the orphan market, including the lack of generic competition for all such drugs, and the price drop modeled is only an assumption. There may be variability in the price drop specifically for the orphan market that is different from the cancer market.

Furthermore, there may be delays in generic entry beyond the 12-month timeframe noted from the economic model framing hypotheses established by Conti and Berndt [6, 10]. However, this issue is less of a concern since the cited model averages delayed generic entry into the total estimate, including instances of "pay for delay" [16]. According to Aitken and colleagues, it should be noted that not all drugs face generic competition upon loss of exclusivity even though generic competition may disproportionately impact the orphan drug market given financial incentives [17]. Grabowski and Kyle also note that drugs in smaller markets (e.g., orphan markets) are less likely to face competition [18]. However, the particular drugs modeled in the budget impact analysis, which have some of the longest periods of extended exclusivity, happen to be "blockbuster" drugs which impact larger segments of patient populations and would otherwise likely have increased competition in an open market with generic and biosimilar alternatives.

Lastly, we only based our budget impact on the size of the cohort associated with claims that a manufacturer filed with the FDA. In reality, not all patients in rare disease cohorts are able to take an indicated orphan drug due to issues with tolerability, etc. Unfortunately, the IQVIA claims did not report prescriptions for all patients in a rare disease cohort either. Future research would benefit from a budget impact analysis linking orphan drug prescribing patterns with all patients in a particular rare disease cohort.

4.2 Policy Recommendations

One possibility is to limit the number of additional exclusivity periods a single drug can receive through the FDA. Since drugs appear to be gaining 7 + additional years of exclusivity after the third orphan drug approval, limiting the exclusivity period to 14 years could spur sufficient innovation and additional testing of the drug for new populations, but still allow for the drug to potentially have generic versions over time. However, the budget impact of exclusivity through the *Orphan Drug Act* does not necessarily suggest that a policy change in this direction is justifiable based on societal cost to the USA alone.

In order to spur additional testing on new populations, the act could allow pharmaceutical companies to receive tax credits for additional clinical trials after the second market exclusivity period ends. Thus, manufacturers of orphan drugs would continue to receive public investment in innovation up front, but their window to profit from branded prices on these drugs would be restricted to a defined time period. Additional economic modeling is required to test this hypothesis.

Perhaps simpler is for the FDA to stop granting approvals when the total patient population exceeds 200,000 people. Since several of the drugs in Fig. 2 have total cohorts across multiple indications exceeding this amount, there may be enough users such that generic competition would not dilute the profitability of a rare disease market.

5 Conclusions

Limiting the total number of rare disease approvals or overall years that a pharmaceutical can benefit from the *Orphan Drug Act* could provide some savings in the billions of dollars with respect to the availability of generics or biosimilars at lower prices. Excess costs of this magnitude could be impacting patient accessibility to life-saving treatments. However, doing so could impact future innovations and discovery of drugs for rare diseases, thereby limiting our knowledge and the evidence for effective treatments and limiting the prescription of drugs to treat certain rare diseases to off-label use. There is questionable risk as to whether the total of about US$600 billion in orphan expenditures

for questionable exclusivity practices is worth the price of innovation across all orphan drugs.

Acknowledgements The authors acknowledge funding from Arnold Ventures to conduct this study. We wish to thank John Shin for his collaborative work related to this study.

Author Contributions Each author contributed to the study as follows: conceptualization and design: WP, GA, RC; data acquisition and analysis: WP, SP, MS, RC; interpretation of the findings: WP, GA, SP, MS, RC; writing and editing of the manuscript: WP, GA, SP, MS, RC. All authors had access to the data at all times.

Data Availability Statement The budget impact model used in this analysis contains the aggregate information from the FDA on orphan disease populations, as well as patient costs from IQVIA claims. This model and these data are available as supplementary material for readers.

Compliance with Ethical Standards

Funding The authors were supported by an unrestricted grant from Arnold Ventures foundation to Johns Hopkins University to conduct this investigation.

Conflict of interest The authors, WP, SP, MS, RC, and GA, have no perceived conflicts for the submitted research.

References

1. Orphan Drug Act. Public Law 97-414. 97th Congress January; 1983. p. 2049–66.
2. U.S. Food and Drug Administration. General Provisions of the Orphan Drug Act. U.S. Code of Federal Regulations: 21 CFR 316. 1992.
3. U.S. Tax Cuts and Jobs Act. Public Law 115-97. In: December tC, editor. 2017.
4. Reaves ND. A model of effective health policy: the 1983 Orphan Drug Act. J Health Soc Policy. 2003;17(4):61–71.
5. Caton ML. Maryland's Prescription Drug Affordability Board Bill set to take effect. The National Law Review. 2019.
6. Conti RM, Berndt ER. Specialty drug prices and utilization after loss of US patent exclusivity, 2001–2007: National Bureau of Economic Research (NBER); 2014.
7. FDA Search Orphan Drug Designations and Approvals. Silver Spring, MD: US Food and Drug Administration (FDA). 2017. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/. Accessed 23 May 2017.
8. FDA/CDER Small Business and Industry Assistance. Patients and exclusivity. Silver Spring, MD: US Food and Drug Administration (FDA). 2015 May 19. https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf. Accessed 25 Feb 2018.
9. Centers for Medicare & Medicaid Services. Consumer Assessment of Healthcare Providers & Systems (CAHPS). https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/CAHPS/. Accessed 5 May 2016.
10. Padula WV, Larson RA, Dusetzina SB, Apperley JF, Hehlmann R, Baccarani M, Eigendorff E, Guilhot J, Huilhot F, Mahon FX, Martinelli G, Mayer J, Muller MC, Niederwieser D, Saussele S, Schiffer CA, Silver RT, Simonsson B, Conti RM. Cost-effectiveness of tyrosine kinase inhibitor treatment strategies for chronic myeloid leukemia in chronic phase after generic entry of imatinib in the United States. J Natl Cancer Inst. 2016;108(7):djw003.
11. Li X, Guh D, Lacaille D, Esdaile J, Anis AH. The impact of cost sharing of prescription drug expenditures on health care utilization by the elderly: own- and cross-price elasticities. Health Policy (Amsterdam, Netherlands). 2007;82(3):340–7.
12. Kesselheim AS. Ethical considerations in orphan drug approval and use. Clin Pharmacol Ther. 2012;92(2):153–5.
13. Sarpatwari A, Beall RF, Abdurrob A, He M, Kesselheim AS. Evaluating the impact of the Orphan Drug Act's seven-year market exclusivity period. Health Aff (Project Hope). 2018;37(5):732–7.
14. Grabowski HG, Long G, Mortimer R. Recent trends in brand-name and generic drug competition. J Med Econ. 2014;17(3):207–14.
15. Thorat C, Xu K, Freeman SN, Bonnel RA, Joseph F, Phillips MI, Imoisilli MA. What the Orphan Drug Act has done lately for children with rare diseases: a 10-year analysis. Pediatrics. 2012;129(3):516–21.
16. Kesselheim AS, Murtagh L, Mello MM. "Pay for delay" settlements of disputes over pharmaceutical patents. N Engl J Med. 2011;365(15):1439–45.
17. Aitken M, Kleinrock M. Orphan Drugs in the United States (part two): exclusivity, pricing and treatment populations. Danbury: The IQVIA Institute; 2018.
18. Grabowski HG, Ridley DB, Schulman KA. Entry and competition in generic biologics. Manag Decis Econ. 2007;28(4–5):491–502.