

POLICIES AND PRICE CONTROLS ON THE RESEARCH AND  
DEVELOPMENT OF ORPHAN DRUGS IN  
THE UNITED STATES AND  
THE EUROPEAN UNION

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by

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## ABSTRACT

### Policies and Price Controls on the Research and Development of Orphan Drugs in the United States and the European Union

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There is substantive literature surrounding the impact of price controls on the research and development (R&D) of new pharmaceutical products. The European Union (EU) and United States (US) are often studied in contrast to examine the influence of price controls as the US has fewer pharmaceutical price controls than the EU.

We find moderate evidence that the US spent more on annual domestic pharmaceutical R&D than the EU between 2004 and 2021, on average, before and after adjusting for GDP growth per capita and year. We find strong evidence that the US increased annual R&D spending at a faster rate than the EU between 2004 and 2021, on average, before and after adjusting for GDP growth per capita.

Prior studies have asserted that increased US R&D spending leads to the production of more pharmaceutical products. Our study aims to quantify the differences in US and EU orphan drug development. Orphan drugs are pharmaceutical products that treat rare diseases. Both the EU and US aim to stimulate orphan drug production with policies including national grants, tax credits, and extended periods of market exclusivity.

Our study gives indication that these policies in the US and EU are effective at spurring rare disease drug creation. We find evidence that orphan drug market authorizations increased annually, on average, in both the US and EU from 2004 to 2021, before and after adjusting for GDP growth rate per capita and the interaction between year and region. We find the same when isolating market authorizations for new orphan drugs.

The US awarded more annual orphan drug market authorizations and market authorizations for new orphan drugs than the EU every year from 2004 to 2021, except in 2007. We find evidence that from 2004 to 2021, the US awarded more annual orphan

drug market authorizations and market authorizations for new orphan drugs than the EU, on average, before and after adjusting for GDP growth per capita and year. There is also evidence that the US increased the number of these authorizations at a faster rate annually than the EU, on average, before and after adjusting for GDP growth per capita.

Our results suggest an association between EU price controls and reduced pharmaceutical innovation. This is seen in the form of less annual R&D spending growth, orphan drug market authorizations, and new orphan drugs compared to the US. However, the benefits of this innovation may not reach patients, as US consumers pay higher pharmaceutical prices due to limited price controls. This contributes to the expansion of health inequities in the US. We are also unsure if the quality of US innovation exceeds that of the EU and if increased innovation is truly the result of lower price controls.

Keywords: Orphan Drugs, Pharmaceutical Research and Development, European Union, United States, Time Series Analysis, Generalized Linear Models, Newey-West Estimator

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## Chapter 1

### INTRODUCTION

The United States is the only major pharmaceutical market where prices are largely unregulated. In every other major market, prices are regulated either directly or indirectly (Abbott & Vernon, 2005). The relationship between price controls and reduced research and development (R&D) spending has been studied extensively; however, most of these studies concluded before 2007. Many studies have examined how increased R&D spending in the United States translates to a greater number of new medicines sold to patients (Mulcahy, 2024). Few studies have evaluated whether patients in the United States also reap the benefit of more orphan drugs, pharmaceutical products that treat rare diseases (Orphanet, *About Orphan Drugs*, n.d.).

We aim to first investigate whether the negative relationship between price controls and R&D spending continues to exist in recent years by studying the differences in R&D spending in the United States (US) and the European Union (EU). We then quantify the differences in US and EU rare disease drug innovation by analyzing the counts of market authorizations for orphan drugs in both regions.

Market authorizations (MAs) are given to orphan drugs that are approved for sale in the US and/or the EU by the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA), respectively. Lastly, because it is possible for an orphan drug to have multiple market authorizations, we model the EU and US' counts of new orphan drugs that have not been previously granted a market authorization for other rare diseases.

## Chapter 2

### LITERATURE REVIEW

In 2007, Abbott and Vernon wrote that, “Economic theory is unambiguous in its prediction that pharmaceutical price controls in the United States will diminish the incentives to invest in new drug R&D” (p. 29). We aim to evaluate this assertion in our paper by performing similar analyses on R&D spending from 2004 to 2021.

We also investigate differences in orphan drug production in the US and EU. Studies have focused primarily on prices of orphan drugs and costs of development. Our study aims to investigate the number of orphan drugs authorized for sale in each respective market.

#### **2.1 Price Controls on Pharmaceutical R&D**

In the United States, pharmaceutical prices are largely unregulated. In all other major pharmaceutical markets, specifically in the European Union, prices are regulated through price caps on products, profit controls, and limits on insurers’ reimbursement levels (Abbott & Vernon, 2005; Gross et al., 1994).

Thus, companies that sell more pharmaceutical products outside the US market face more price regulations. The U.S. Department of Health and Human Services (2024) found that, in 2022, US prescription drug prices were approximately 2.78 times higher than prices in 33 Organization for Economic Cooperation and Development (OECD) comparison countries.

Lower prices make existing lifesaving and quality-of-life-improving medicines more accessible to patients, but they also lead to reduced pharmaceutical company

profits. Vernon (2003) found that pre-tax profits in the United States are, on average, approximately four times as large as those in non-US markets. A reduction in profits may lead to reduced spending on the R&D of new pharmaceutical products.

Vernon (2004) explained that current cash flows and future profit expectations spur pharmaceutical R&D. Through studies of R&D in the EU and US, Golec & Vernon (2006) found that, in 1986, EU pharmaceutical R&D spending was about 24 percent higher than US spending. By 2004, US spending exceeded EU spending by about 15 percent. Between 1993 and 2004, US R&D spending exceeded EU R&D spending every year.

Shaikh et al. (2020) used the proportion of a pharmaceutical company's market share in the European Union to its market share in the United States to represent its exposure to price controls. Shaikh et al. (2020) and Vernon (2004) represented R&D intensity as the ratio of R&D expenditure to total sales. Shaikh et al. (2020) found a negative association between EU market share and R&D intensity. However, this result was not statistically significant when accounting for firm fixed effects including mergers, acquisitions, and number of employees.

Golec & Vernon (2006) note that firms typically report only total R&D spending rather than domestic and international spending separately, complicating firm-level pharmaceutical spending analysis. They explain that many firms have moved their operations from the EU to the US due to greater sales in the US. There are also requirements that firms perform parts of the clinical trial process in the US and US-based trials help firms establish relationships with US physicians who set prescription standards (Golec & Vernon, 2006). To account for this, they used data from The Pharmaceutical

Research and Manufacturers of America (PhRMA) and The European Federation of Pharmaceutical Industries and Associations (EFPIA), who report total and domestic R&D spending for their members by year. We used this data to perform our analysis of domestic R&D spending in the EU and US.

Increasing R&D spending is impactful as the price to develop new pharmaceuticals is high. The average R&D cost of developing a new drug is estimated to be between 327 to 773.2 million US dollars, including the costs of products that fail during the development process (Sertkaya et al., 2024).

Our study aims to investigate how pharmaceutical R&D spending differs between the US and EU as an indicator of how price controls are associated with innovation. We also perform the same analysis on the number of orphan drugs produced in the US and EU. Orphan drug production may have a differing relationship with price controls than overall R&D spending due to existing policies and market realities.

## **2.2 Orphan Drugs for Rare Diseases**

Orphan drugs are medicines that target rare diseases. Rare diseases affect approximately one in ten people in the US (Johns Hopkins Medicine, 2024). However, pharmaceutical treatments for rare diseases have been historically underdeveloped because few individuals are affected by each rare disease or condition (U.S. Food and Drug Administration, 2018).

Orphan drugs can be more difficult to develop than other pharmaceuticals because of limited knowledge of rare diseases, reduced numbers of patients to enroll in clinical trials, and the need to deviate from traditional study designs (Milne & Cabanilla, 2007).

When these drugs are sold, there is a thinner market to recoup development costs because of the smaller number of patients with these diseases. As a result, firms charge higher prices for these products. Simoens (2011) found a negative association between the prevalence of a disease and the cost of its treatment.

In the United States, these prices are even higher. Similar to the overall pharmaceutical market, Żelewski et al. (2022) found that prices of orphan drugs are higher in the United States than in six selected European Union countries. The average price ratio was 1.64.

To spur the growth of the rare disease drug market, the US implemented legislation to regulate and incentivize orphan drug production through the 1983 US Orphan Drug Act (U.S. Food and Drug Administration, 2018). The EU mirrored the US' approach with the 1999 Regulation (EC) No 141/2000 of the European Parliament and of the Council (Publications Office of the European Union, 2000). Other countries including Japan, Canada, Singapore, China, South Korea, Taiwan, and Australia also adopted policies aiming to spur the development of rare disease drugs (Chan et al., 2020).

In the United States, orphan drugs are classified as pharmaceutical products that treat a disease or condition that affects less than 200,000 people in the US (U.S. Food and Drug Administration, 2018). In the European Union, orphan drugs treat diseases or conditions that affect less than 5 in 10,000 people in the EU (European Medicines Agency, n.d.).

In the European Union, drugs with an orphan designation are allowed a 10-year market exclusivity period, which can be extended by 2 years if pediatric development is included. This period may be reduced to 6 years if the product is sufficiently profitable.

The EU also provides free scientific advice during the development process and monetary incentives including national grants and reduced or waived regulatory fees for firms producing orphan drugs. In the United States, drugs with an orphan designation are allowed a 7-year market exclusivity period plus 6 months of exclusivity for qualified pediatric studies. Firms that produce orphan drugs also receive free scientific advice, reduced or waived regulatory fees, tax credits on clinical trials, and specific subsidies for clinical trials. Additionally, both the EU and US have pathways for accelerated approval of orphan drugs which meet a sufficient level of public health importance and innovation (Hall & Carlson, 2014).

In the United States, orphan drug policy includes the Orphan Drug Tax Credit (ODTC), that allows firms to receive a tax credit for 50 percent of qualified clinical trial costs for new orphan drugs. “From 1983 through 2014, it is estimated that 67 fewer approved orphan drugs would have been on the market without the ODTC” (Biotechnology Industry Organization and the National Organization for Rare Disorders, 2015, pp. i-ii). In 2017, this tax credit was reduced from 50 percent to 25 percent of clinical trial costs (Austin & Hayford, 2021).

In the European Union, monetary benefits vary between countries. For example, in Belgium, orphan drugs are exempt from a national pharmaceutical tax, pricing and reimbursement is faster, and some public funding is provided. In Croatia, orphan drugs and other expensive medicines are financed through a dedicated fund (Horgan et al., 2022).

Table 2.1 is a timeline of selected notable legislation which have enacted these orphan drug policies in the US and EU. This table is not an exhaustive list of all orphan drug legislation and does not contain many general pharmaceutical policies that may impact orphan drug production.

**Table 2.1 Timeline of Orphan Drug Legislation in the US and EU**

<b>Year</b>	<b>EU Legislation</b>	<b>US Legislation</b>
1983		<b>Orphan Drug Act</b> Tax credits, a waiver of the Prescription Drug User Fee, and extended market exclusivity are offered to firms for the production of orphan drugs in the United States (Roberts & Wadhwa, 2021).
1985-1990		<b>1985 and 1990 amendments of the Orphan Drug Act</b> Biologics, medical devices and medical foods are included in the definition of an orphan product (Orphanet, <i>Orphan Drugs in the United States of America</i> , n.d.).
1992		<b>1992 amendment of the Orphan Drug Act</b> For orphan drugs that are similar to currently authorized drugs, a firm must demonstrate the clinical superiority of the new product to receive an orphan designation. More than one sponsor can receive an orphan designation for the same drug. Market exclusivity is given to the first firm to file a new drug application. Designated orphan drugs may be sold by competitors during the period of market exclusivity for diseases outside of those the original firm has a designation for (Orphanet, <i>Orphan</i>



		<i>Drugs in the United States of America, n.d.).</i>
2000	<p><b>Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products</b></p> <p>This regulation offers protocol assistance, extended market exclusivity and research grants for orphan drugs in the European Union (Publications Office of the European Union, 2000).</p>	
2004	<p><b>Regulation (EC) No 726/2004 of the European Parliament and of the Council of March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency</b></p> <p>When a marketing authorization application is submitted for a medicinal product with major public health and innovation interest, the applicant may request an accelerated assessment procedure (European Parliament, Council of the European Union, 2004).</p>	
2006	<p><b>Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric use</b></p> <p>The market exclusivity period may be extended from ten to twelve years if pediatric use is studied sufficiently (Publications Office of the European Union, 2006).</p>	

2012		<b>Food and Drug Administration Safety and Innovation Act</b> Expedites the development and review of new drugs that have preliminary clinical evidence that indicate substantial improvement over current treatments for patients with serious or life-threatening diseases. Such a drug is referred to as a “breakthrough therapy” (Hall & Carlson, 2014).
2017		<b>2017 Tax Act</b> This act reduced tax credits awarded to orphan drugs from 50 percent of clinical trial costs to 25 percent (Austin & Hayford, 2021; U.S. Government Publishing Office, 2018).

While orphan drugs may be more difficult to develop due to clinical trial restraints and lack of knowledge, orphan drug policies and development practices can make them cheaper to develop than other pharmaceutical products. In a study of 100 randomly selected orphan drugs and 100 randomly selected non-orphan drugs approved by the United States Food and Drug Administration (FDA) between January 2000 to December 2015, the observed average total R&D cost required per market success for an approved orphan drug was \$166 million (2013 USD) compared to \$291 million per non-orphan drug (Jayasundara et al., 2019). Tax credits can account for some of this difference, as well as the use of small sample sizes in clinical trials (Côté & Keating, 2012).

Additionally, Grabowski and Vernon (1990) found that pharmaceutical product returns decline sharply after patent expiration due to competition with generics. This suggests that longer market exclusivity periods increase returns on orphan drugs. We hypothesized that longer periods of orphan drug market exclusivity in the EU may lead to

more orphan drug production in the EU than the US, although this was not the finding of our statistical analysis.

The provision of orphan drug incentives and benefits including reduced costs, market exclusivity, and monetary incentives may result in a different trend of development compared to that of all pharmaceutical products.

## Chapter 3

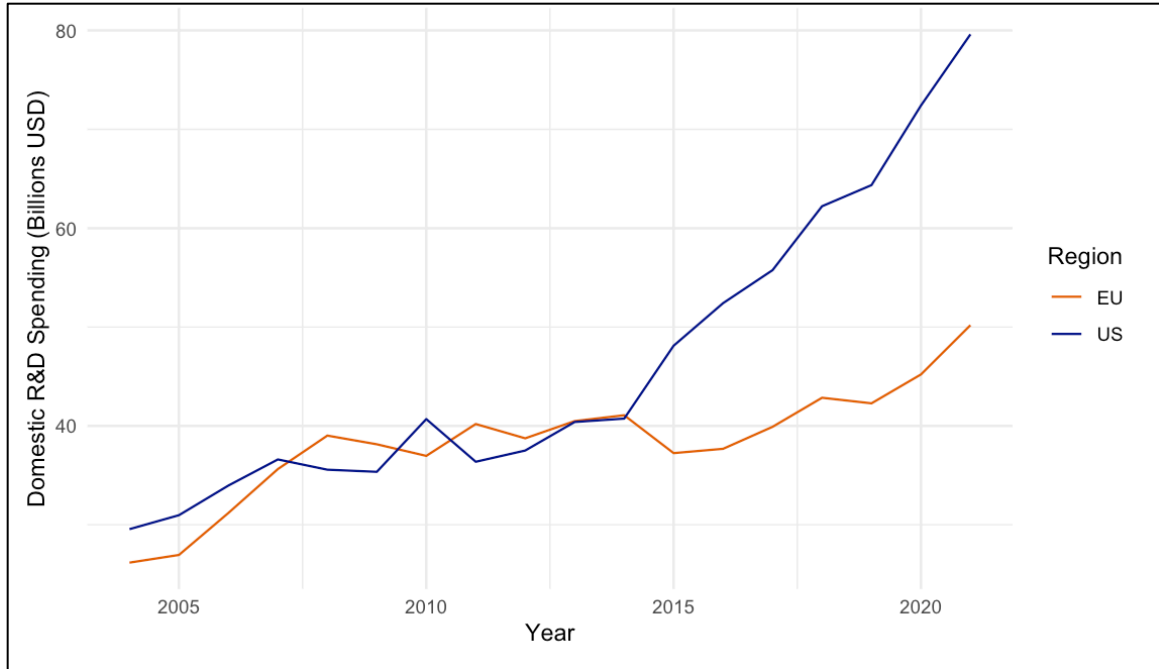
### METHODS

#### **3.1 Domestic Pharmaceutical R&D Spending**

We first investigate the differences in US and EU pharmaceutical R&D spending from 2004 to 2021. We perform our analysis of R&D spending using annual EFPIA and PhRMA member data (European Federation of Pharmaceutical Industries and Associations, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023; Pharmaceutical Research and Manufacturers of America, 2022). We model domestic R&D spending rather than overall R&D spending to account for firms spending in both the EU and US. There is one observation for each year in the US and the EU from 2004 to 2021 (36 total observations). 2011 EFPIA spending was not available, so it was imputed with the average of EFPIA spending in 2010 and 2012 in euros.

EU R&D spending was converted from euros to US dollars using the annual average closing exchange rate (Macrotrends, *Euro Dollar Exchange Rate (EUR USD) - Historical Chart*, 2024). Spending amounts are measured in billions of US dollars. In our models, 2004 is coded as year 0. Golec and Vernon's similar 2006 study of domestic R&D spending from 1986 to 2004 had a one year longer study period than our analysis.

Figure 3.1 shows EFPIA and PhRMA member pharmaceutical domestic R&D spending. This spending is referred to as EU and US R&D spending throughout this report.



**Figure 3.1 Annual Domestic R&D Spending in the EU and US**

*EU domestic R&D spending in 2011 is imputed with the average of EU spending in 2010 and 2012 in euros because this data was not available. EU spending is converted from euros to US dollars based on the annual average closing exchange rate.*

Golec & Vernon (2006) observe that domestic EU R&D spending exceeded that of the US from 1986 to 1997, and US spending exceeded EU spending from 1998 to 2004. We can see visually that the US and EU continued to alternate in leading R&D spending until 2014.

In 2014, US R&D spending looks to diverge from EU spending. This coincides with an increase in prescription spending. An overall pharmaceutical price increase occurred in the US and several EU countries in 2014; however, this increase was the most pronounced in the US (Sarnak et al., 2017). We do not study this 2014 increase in price, but this observation aligns with our conjecture that increased prices may lead to increased R&D spending.

We analyze the average difference in domestic R&D spending in the US and EU by performing six linear regressions of R&D spending with different combinations of explanatory variables: years after 2004, region (US and EU), annual GDP growth rate per capita, polynomial transformations of the years after 2004 variable and interactions between year and region variables. Annual GDP growth rate per capita is used to capture and control for the overall economic performance of the US and EU (Macrotrends, *European Union GDP per Capita 1970-2024*, 2024; Macrotrends, *U.S. GDP per Capita 1960-2024*, 2024). A polynomial transformation of the years after 2004 variable is included to capture the visual nonlinearity in R&D spending.

The full model with all predictors is as follows:

$$\begin{aligned} \widehat{\text{Annual R\&D Spending}}_{t,region} &= \hat{\beta}_0 + \hat{\beta}_1 x_{region} + \hat{\beta}_2 (\text{GDP growth rate per capita})_{t,region} + \hat{\beta}_3(t) \\ &+ \hat{\beta}_4(t^2) + \hat{\beta}_5(t \times x_{region}) + \hat{\beta}_6(t^2 \times x_{region}) \end{aligned}$$

Where:

$t$  is number of years after 2004. This is referred to as years throughout our analysis.

$region$  specifies if the observation is from the US or EU.

$$x_{region} = \begin{cases} 0, & region = EU \\ 1, & region = US \end{cases}.$$

$(\text{GDP growth rate per capita})_{t,region}$  is the annual GDP growth rate per capita,  $t$  years after 2004 for the specified region.

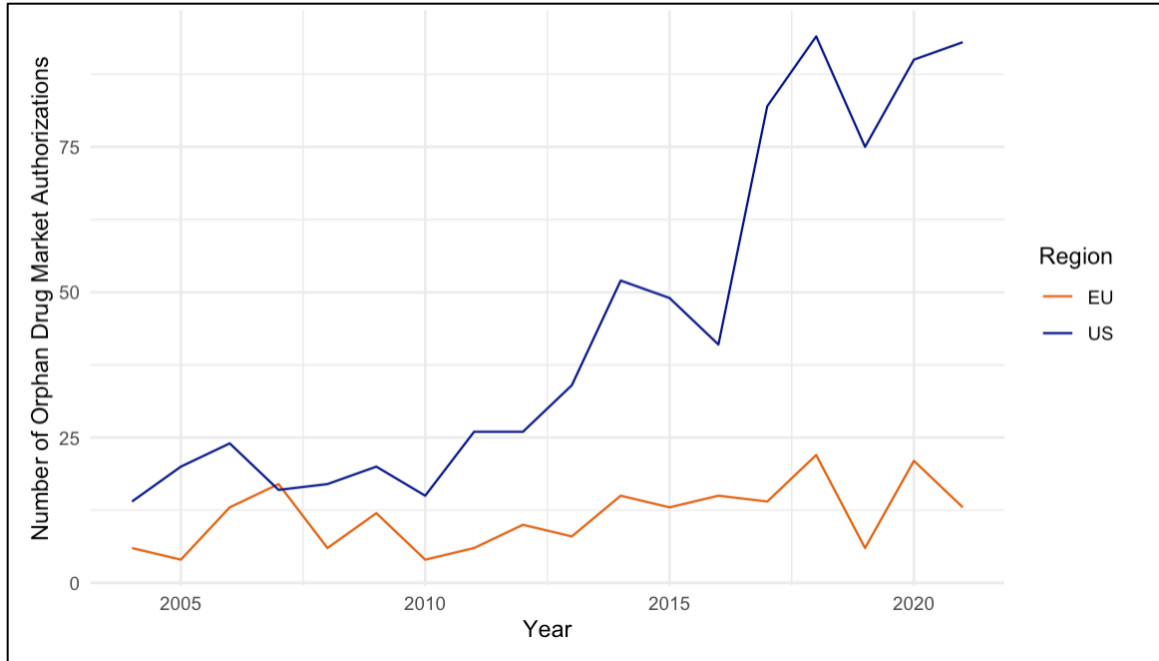
We test models with different combinations of these predictor variables to analyze if our coefficient estimates are robust to variable additions. We compared model

performance using the Akaike Information Criterion (AIC) which measures the goodness of fit of our model while penalizing complex models with more parameters (Sukumar, 2024). This assessment of coefficient robustness, and AIC-based comparison process is used in all modeling performed in this study.

### **3.2 Orphan Drug Market Authorizations**

Next, we analyze the difference in the annual number of market authorizations for orphan drugs in the US and EU. These are approvals by the US Food and Drug Administration or European Medicines Agency for orphan drugs to be sold to treat a specific disease or condition. Because of policies incentivizing the production of orphan drugs, it is uncertain whether the number of market authorizations in the US and EU follows the same trend as overall domestic R&D. The total number of market authorizations for orphan drugs to be sold in the EU and US is counted by year. Market authorization data for the EU are obtained from Orphanet (Orphanet, 2021) and market authorization data for the US are obtained from the FDA (U.S. Food and Drug Administration, 2024).

We visualize the annual number of market authorizations of orphan drugs for sale in the EU and US in Figure 3.2.



**Figure 3.2 Annual Number of Orphan Drug Market Authorizations in the EU and US**

The US awarded more market authorizations for orphan drugs every year between 2004 and 2021, except in 2007. The US looks to increase annual orphan drug market authorizations at a faster rate than the EU.

We perform five Poisson regressions of the annual number of orphan drug market authorizations with different combinations of explanatory variables: years after 2004, region (US and EU), GDP growth per capita, and interactions between year and region.

We used Poisson generalized linear models due to the count nature of the data (count of orphan drug market authorizations). Poisson models typically represent the distribution of counts well as they restrict the response to be positive. They also allow for a curved, non-linear relationship between explanatory and response variables because a log link function is used (Anderson, n.d.).

The full model with all predictors and interactions, is as follows.



$$\begin{aligned}
& \log (\widehat{\text{Average annual orphan drug market authorization}}_{S_{t,region}}) \\
&= \hat{\beta}_0 + \hat{\beta}_1 x_{region} + \hat{\beta}_2 (\text{annual GDP growth rate per capita})_{t,region} \\
&+ \hat{\beta}_3(t) + \hat{\beta}_4(t \times x_{region})
\end{aligned}$$

with the same variable descriptions as our linear models of R&D spending.

### 3.3 Market Authorizations for New Orphan Drugs

It is possible for firms to receive multiple market authorizations for the same drug if they can demonstrate it may be used to treat another condition (Miller et al., 2022). There are 223 orphan drugs in the US with more than one orphan drug market authorization. Table 3.1 presents a list of US drugs with more than five orphan drug market authorizations. This table does not include market authorizations for non-rare diseases.

**Table 3.1 Counts of US Drugs with More Than Five Orphan Drug Market Authorizations**

Generic Name	Market Authorizations
nivolumab	16
pembrolizumab	16
bevacizumab	11
ibrutinib	11
ivacaftor	11
olaparib	11
lenalidomide	9
lisocabtagene maraleucel	9
adalimumab	8
axicabtagene ciloleucel	7
brentuximab vedotin	7
crizotinib	7
daratumumab	7
ravulizumab-cwvz	7
zanubrutinib	7
canakinumab	6
isavuconazonium sulfate	6
rituximab	6
selpercatinib	6

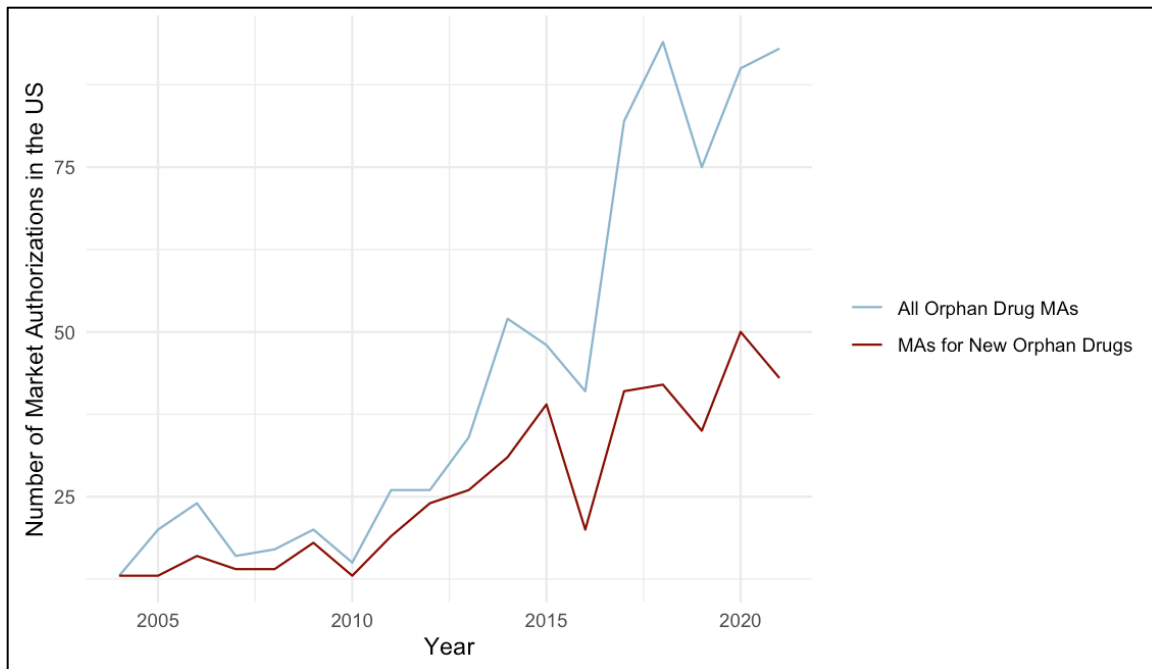
In contrast, in the EU, there are nine orphan drugs with over one market authorization. Table 3.2 presents a list of EU drugs with more than one orphan drug market authorization. This table does not include market authorizations for non-rare diseases.

**Table 3.2 Counts of EU Drugs with More Than One Orphan Drug Market Authorization**

Generic Name Market Authorizations	
glivec	6
nexavar	3
revlimid	3
carbaglu	2
soliris	2
torisel	2
tracleer	2
yondelis	2
zavesca	2

Because of this discrepancy between the US' and EU's tendencies to re-market authorize orphan drugs, we want to study market authorizations for new orphan drugs in the US and EU. These are drugs that are receiving an orphan drug market authorization for the first time in the year counted.

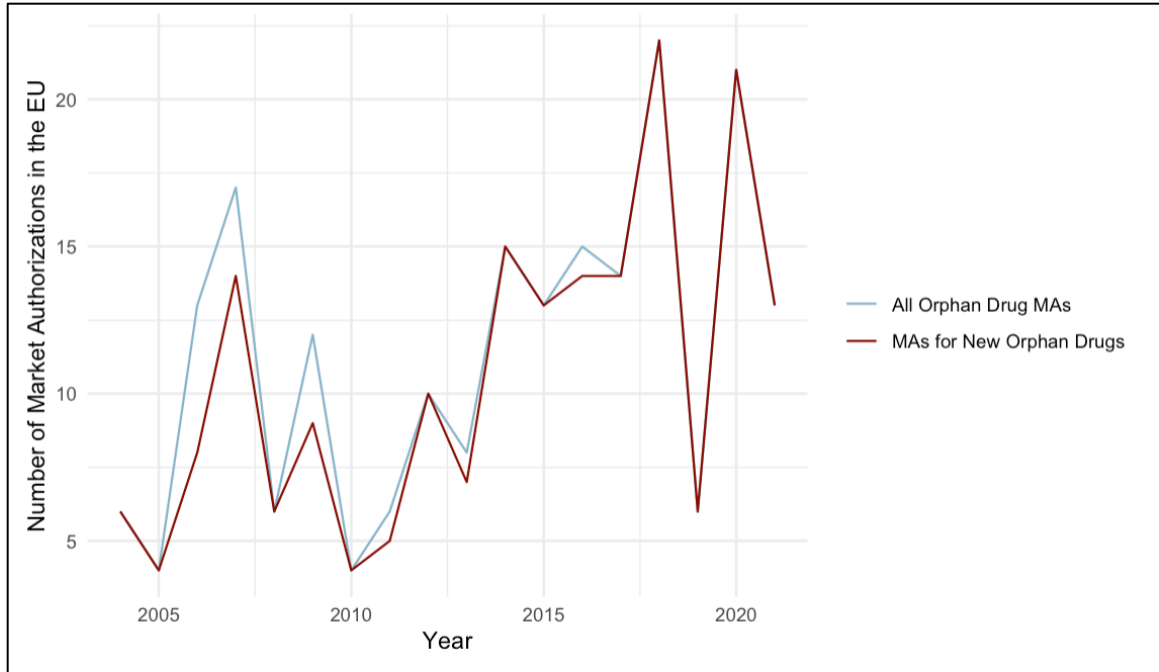
Figure 3.3 shows the annual counts of all market authorizations compared with the annual counts of market authorizations for new orphan drugs in the US.



**Figure 3.3 Annual Number of Orphan Drug Market Authorizations in the US**

There is a visual difference in the trend of orphan drug market authorizations overall and market authorizations for new orphan drugs in the US in Figure 3.3.

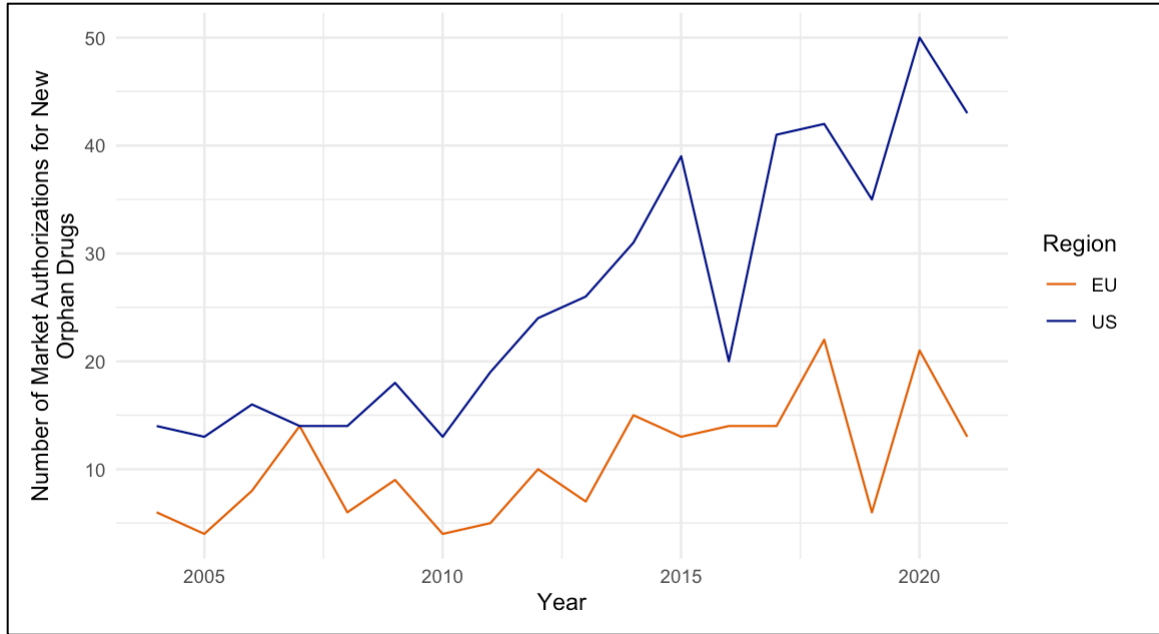
Figure 3.4 shows the annual counts of all market authorizations compared with the annual counts of market authorizations for new orphan drugs in the EU.



**Figure 3.4 Annual Number of Orphan Drug Market Authorizations in the EU**

Because there are fewer products with multiple orphan drug market authorizations in the EU, there is not as large of a visual difference in the trend between orphan drug market authorizations overall and market authorizations for new orphan drugs.

Figure 3.5 shows the counts of orphan drug market authorizations for pharmaceuticals that have not had an orphan drug market authorization in the past in the US and EU. It is notable that these counts of market authorizations for new orphan drugs may include drugs that have been previously granted a market authorization for non-rare conditions.



**Figure 3.5 Annual Number of Market Authorizations for New Orphan Drugs in the EU and US**

The US still awarded more annual market authorizations for new orphan drugs than the EU in every year between 2004 and 2021, except in 2007. However, the slopes of US and EU authorizations over time look more similar in Figure 3.5 than US and EU slopes of all orphan drug market authorizations in Figure 3.2.

We followed the same procedure as discussed in section 3.2 of modeling using Poisson generalized linear models. Our response variable is now the average annual number of market authorizations for new orphan drugs.

### 3.4 Model Assumptions

#### 3.4.1 Low Collinearity of Predictors

Variance inflation factors (VIFs) are calculated for all model main effects including R&D spending as a potential predictor of orphan drug market authorizations. We find that years and R&D spending have VIFs greater than 2 when simultaneously

used as predictors of orphan drug market authorizations. VIFs are listed in appendix C.1 and C.2. After modeling R&D spending by time and region in section 4.1, we find that region and time appear to be correlated with R&D spending. Further visualizations of our predictors show potential collinearity between region and R&D spending because R&D spending is typically higher in the US compared to the EU. Appendix Figure C.1 visualizes this relationship. We can also view the correlation between years and R&D spending in Figure 3.1 as R&D spending looks to increase over time.

Because of R&D spending's potential collinearity with year and region, we do not fit regressions using R&D spending as a predictor. When predictors are correlated, standard errors become inflated and model inference is inaccurate (Kim, 2019).

### **3.4.2 Independence of Residuals and the Newey-West Estimator**

Because we are studying time series data, the regression assumption of independent model residuals is likely violated as observations may be time-dependent. The traditional standard errors for ordinary least squares estimates assume that residuals are independent. We estimate residual autocorrelation using the sample autocorrelation function (ACF) and sample partial autocorrelation function (PACF). If significant autocorrelation exists at any lag greater than lag zero, there is evidence that the assumption of residual independence has been violated.

Because we are studying EU and US spending, we are modeling two separate time series, or panels. Thus, the covariance of residuals must be calculated separately for each panel, and we should visualize EU and US residual plots separately. An example of a residual panel is shown in appendix Figure C.2.

To adjust standard errors for residual autocorrelation, we use the Newey-West estimator. This method assumes that the covariance between observations decreases as the time between observations increases. Standard errors of our coefficient estimates are then adjusted for estimated residual autocovariance. Correcting standard errors leads to more accurate p-values. This method does not change the coefficients of a regression model, only the associated standard errors and p-values.

The Newey-West estimator is the most popular heteroskedasticity and autocorrelation consistent (HAC) estimator in economics and allows for a straightforward adjustment of standard errors (Ao, 2009). The Newey-West estimator is also easily applied to panel data and Poisson generalized linear model residuals (Zeileis & Lumley, 2024). Alternatively, we could explicitly model the autoregressive and moving average (ARMA) nature of our time series. However, estimating ARMA models is a more complex process than adjusting standard errors, especially when data is paneled (Li et al., 2021). We are also only performing inference on our data, not forecasting, so we are not explicitly interested in the results of an ARMA model of our residuals.

### **3.5 Data Representativeness**

Most leading pharmaceutical companies are members of the PhRMA and EFPIA (Pharmaceutical Research and Manufacturers of America, n.d.; European Federation of Pharmaceutical Industries and Associations, n.d.). However, these trade groups do not include all pharmaceutical companies in the US and EU. Thus, differences in these organizations' representations of the EU and US pharmaceutical markets may impact our conclusions when comparing their members' R&D spending.

### 3.6 Software Packages

In R, we use the `lm()` function in the `stats` package to estimate our linear models. We use the `glm()` function in the `stats` package with `family=poisson(link="log")` to estimate our Poisson models.

The `vcovPL()` function in the R `sandwich` package is used to apply Newey-West adjustments to our panel data (Zeileis & Lumley, 2024). All models in our analysis are adjusted using this function.

Code for our full linear model of annual domestic R&D spending and our full Poisson generalized linear model of annual orphan drug market authorizations can be found in appendix D.1 and D.2.



## Chapter 4

### ANALYSIS

#### **4.1 Domestic Pharmaceutical R&D Spending in the US and EU**

The following table shows six linear regressions used to estimate annual domestic pharmaceutical R&D spending from the EFPIA and PhRMA in the EU and US, respectively. Each column of Table 4.1 represents one model. These six models contain different combinations of our predictor variables shown on the left side of the table. This allows us to see how relationships between predictors and the response change with the addition of other predictors. The standard errors of the model coefficients in Table 4.1 have been adjusted using the Newey-West estimator. Unadjusted models are found in appendix Table B.1.

**Table 4.1 Newey-West Adjusted Linear Models of Annual Domestic Pharmaceutical R&D Spending**

	<i>Dependent variable:</i>					
	Annual Domestic Pharmaceutical R&D Spending (Billion USD)					
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
US	7.926* (4.029)	7.926* (4.089)	7.905* (4.128)	-5.998 (4.720)	-5.569 (4.963)	5.530*** (1.495)
Years After 2004		1.765*** (0.207)	1.809*** (0.190)	0.946*** (0.190)	0.996*** (0.216)	1.811** (0.668)
Years After 2004 <sup>2</sup>						-0.048 (0.037)
Annual GDP Growth Rate Per Capita			0.256** (0.115)		0.140 (0.096)	0.116 (0.072)
US:Years After 2004				1.638*** (0.443)	1.586*** (0.464)	-2.595*** (0.550)
US:Years After 2004 <sup>2</sup>						0.246*** (0.030)
Intercept	38.331*** (1.986)	23.332*** (3.177)	22.136*** (3.265)	30.293*** (2.157)	29.417*** (2.612)	27.374*** (2.705)
AIC	281	240	240	218	219	185
RMSE	11	6.09	5.9	4.36	4.29	2.54
Adj R <sup>2</sup>	0.09	0.71	0.72	0.85	0.85	0.94
F Statistic	4.42	44.28	31.14	65.92	49.88	97.43
p-value	0.0431	0	0	0	0	0
<i>Note:</i>	* p<0.1; ** p<0.05; *** p<0.01					

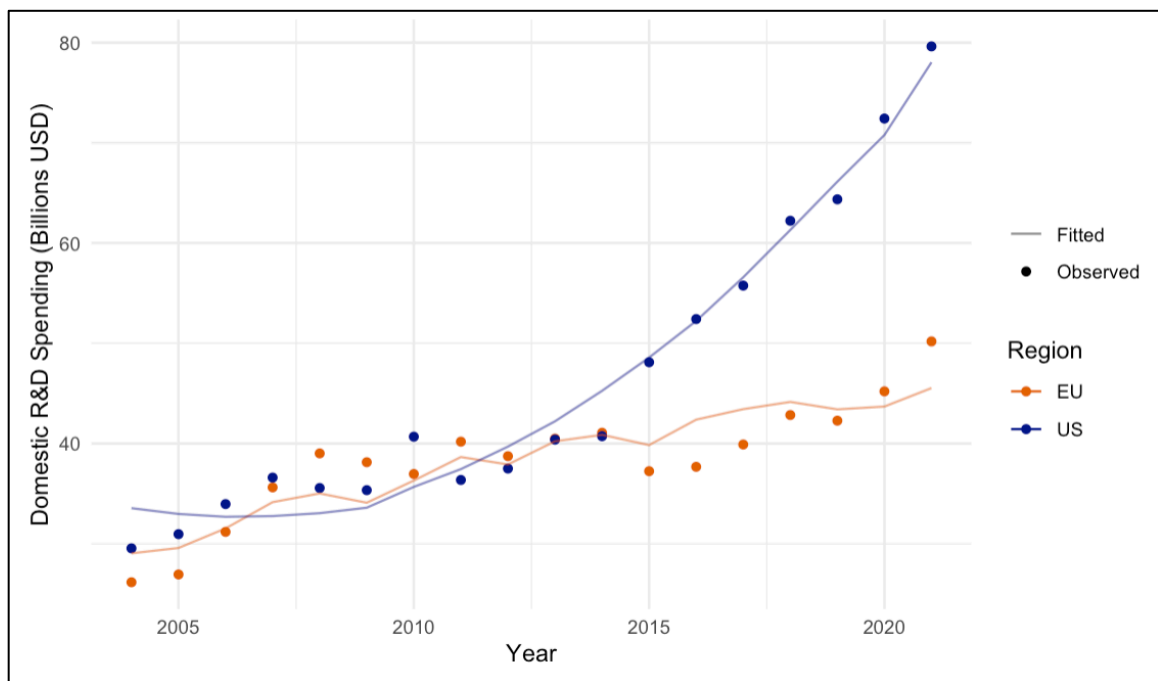
The models listed in Table 4.1 provide moderate evidence that the US spent more than the EU on annual domestic pharmaceutical R&D, on average, after and before adjusting for years after 2004 (henceforth referred to as years) and GDP growth per capita. The US indicator is positive and significant in models 1 through 3, robust to additions of these other predictors.

There is strong evidence that both the US and EU increased annual R&D spending, on average, between 2004 and 2021, after and before adjusting for GDP growth

per capita and the interaction between years and region. There is a positive and significant coefficient for years in every model from 2 through 6.

There is strong evidence that the US increased annual R&D spending at a faster rate annually than the EU, on average, after and before adjusting for GDP growth per capita. The interaction between years and region is positive and significant in models 4 and 5. This coefficient becomes negative when the higher-order term, years squared interacted with the US is added in model 6. This higher order term is positive and significant in model 6, aligning with the conclusion that there is evidence that the US increased annual R&D spending at a faster rate than the EU, on average, after adjusting for GDP growth per capita between 2004 and 2021.

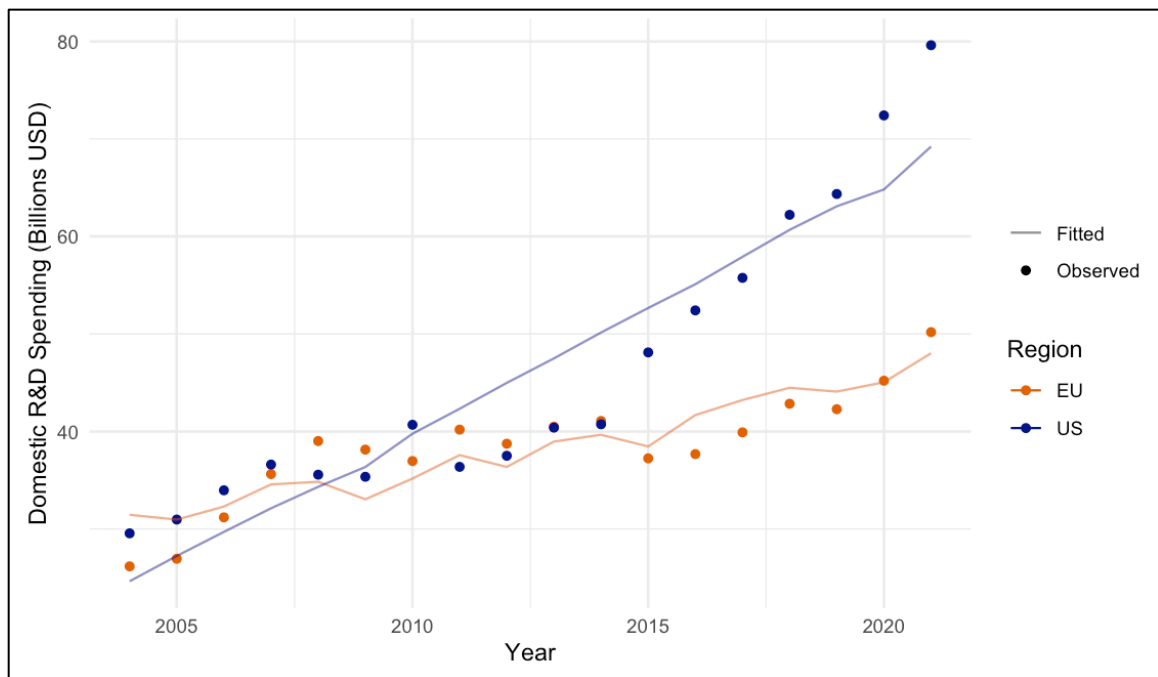
Adding this polynomial transformation of the years term results in a better fit to our data; model 6 has the lowest AIC. Model 6 is pictured below in Figure 4.1.



**Figure 4.1 Linear Model 6 of Annual Domestic R&D Spending**

The model including a polynomial transformation of years, included as a main effect and in the interaction with region, best captures the nonlinearity in domestic R&D spending over time. The other models do not capture this curvature.

The next-best models on a basis of AIC are models 4 and 5. Model 5 is pictured below in Figure 4.2. Model 5 does not contain this polynomial term.



**Figure 4.2 Linear Model 5 of Annual Domestic R&D Spending**

The nonlinearity of spending over time in the US looks to be underrepresented in this model. However, the conclusions of model 5 align with the more complex model 6. Although model 6 fit our data best, it is less interpretable than the other models because of polynomial year terms. Because the less complex models come to similar conclusions as the polynomial model, we use model 3 and 5 to interpret differences in R&D spending.

Without accounting for the differing slopes of R&D spending in the EU and US, we can look at model 3 which only estimates the overall slope of and difference between

average R&D spending in the US and EU from 2004 to 2021. The coefficient for the US indicator in model 3 has a 90% confidence interval of (0.9, 14.9). With 90% confidence, our model estimates that from 2004 to 2021, the US spent between 0.9 and 14.9 billion US dollars more annually than the EU on domestic pharmaceutical R&D on average, after adjusting for GDP growth per capita and year. This may lead to the production of several more pharmaceutical products in the US than the EU annually as Sertkaya et al. (2024) estimates that the average R&D cost of developing a new drug is between 327.0 to \$773.2 million US dollars. However, it is noteworthy that the 95% confidence interval for the US indicator in model 3 contains zero.

The 95% confidence interval for years in model 5 is (0.6, 1.4). With 95% confidence, our model estimates that the EU increased R&D spending between 0.6 and 1.4 billion US dollars annually, on average between 2004 and 2021, after adjusting for GDP growth per capita.

The 95% confidence interval for the interaction between US and years in model 5 is (0.6, 2.5). This is the additional amount that we expect the US to have increased R&D spending annually, on average, compared to the EU between 2004 and 2021, after adjusting for GDP growth per capita. Our model estimates that the US increased R&D spending between 1.2 and 3.9 billion US dollars annually, on average between 2004 and 2021, after adjusting for GDP growth per capita.

These results align with our visual analysis of R&D spending in section 3.1 where we explained that there looked to be a visually larger growth rate in R&D spending for the US compared to the EU.

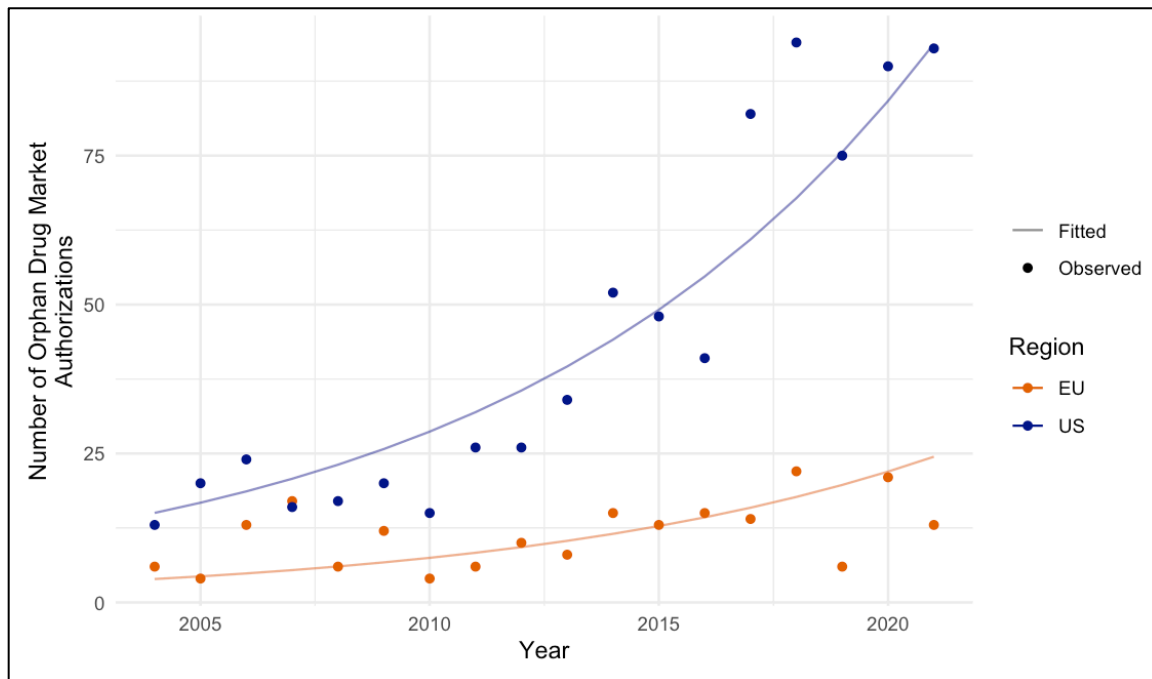
## 4.2 Orphan Drug Market Authorizations

The following table shows five Poisson generalized linear models used to estimate the annual counts of orphan drug market authorizations. The standard errors of the model coefficients in Table 4.2 have been adjusted using the Newey-West estimator. Unadjusted models are found in appendix Table B.2.

**Table 4.2 Newey-West Adjusted Poisson Models of Orphan Drug Market Authorizations**

	<i>Dependent variable:</i>				
	Annual Number of Orphan Drug Market Authorizations				
	Model 1	Model 2	Model 3	Model 4	Model 5
US	1.344*** (0.171)	1.344*** (0.173)	1.339*** (0.178)	0.489** (0.211)	0.507** (0.203)
Years After 2004		0.108*** (0.012)	0.107*** (0.012)	0.046*** (0.017)	0.047*** (0.016)
Annual GDP Growth Rate Per Capita			0.009 (0.014)		0.005 (0.010)
Years After 2004:US				0.080*** (0.017)	0.078*** (0.016)
Intercept	2.433*** (0.123)	1.366*** (0.224)	1.348*** (0.196)	2.014*** (0.218)	1.987*** (0.201)
AIC	554	273	273	250	251
RMSE	20.84	8.34	8.45	7.54	7.63
Log Likelihood	-275.04	-133.55	-132.65	-121	-120.69
<i>Note:</i>	* p<0.1; ** p<0.05; *** p<0.01				

Our model with the lowest AIC and RMSE is model 2, shown below in Figure 4.3.



**Figure 4.3 Poisson Model 2 of Annual Orphan Drug Market Authorizations**

The models listed in Table 4.2 provide evidence that the US awarded more annual market authorizations for orphan drugs, on average, after and before adjusting for years and GDP growth per capita between 2004 and 2021. The US indicator remains significant and positive in models 1 through 3, robust to additions of these other variables.

The US and EU are both estimated to increase orphan drug market authorizations annually on average, after and before adjusting for GDP growth per capita and the interaction between years and region between 2004 and 2021. There is a significant positive coefficient for years in models 2 through 5.

There is evidence that the US increased annual orphan drug market authorizations at a faster pace than the EU, on average, after and before adjusting for annual GDP

growth per capita between 2004 and 2021. The interaction between years and region is positive and significant in models 4 and 5.

### **4.3 Market Authorizations for New Orphan Drugs**

Because we see a visual difference in the number of all orphan drug market authorizations and market authorizations for new orphan drugs, especially in the US, in section 3.3, we perform the same modeling of market authorizations for new orphan drugs.

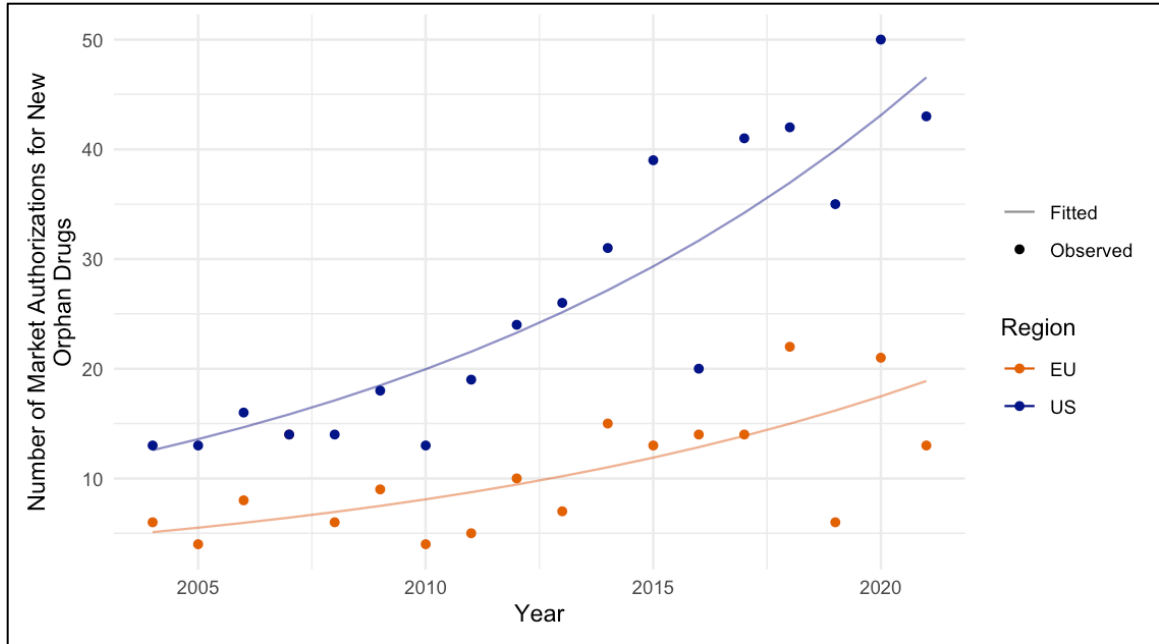
Table 4.3 displays five Poisson generalized linear models used to estimate the annual number of market authorizations for new orphan drugs. The standard errors of the model coefficients have been adjusted using the Newey-West estimator. Unadjusted models are found in appendix Table B.3.



**Table 4.3 Newey-West Adjusted Poisson Models of Market Authorizations for New Orphan Drugs**

	<i>Dependent variable:</i>				
	Annual Number of Market Authorizations for New Orphan Drugs				
	Model 1	Model 2	Model 3	Model 4	Model 5
US	0.903*** (0.081)	0.903*** (0.082)	0.901*** (0.086)	0.667*** (0.169)	0.669*** (0.163)
Years After 2004		0.077*** (0.007)	0.077*** (0.007)	0.061*** (0.014)	0.061*** (0.015)
Annual GDP Growth Rate Per Capita			0.002 (0.011)		0.001 (0.010)
Years After 2004:US				0.023* (0.013)	0.022* (0.013)
Intercept	2.362*** (0.145)	1.629*** (0.117)	1.624*** (0.107)	1.794*** (0.181)	1.789*** (0.175)
AIC	314	215	217	216	218
RMSE	9.39	4.71	4.74	4.64	4.66
Log Likelihood	-155.15	-104.75	-104.71	-103.88	-103.87
<i>Note:</i>			* p<0.1; ** p<0.05; *** p<0.01		

Our model with the lowest AIC and RMSE is model 2, shown below in Figure 4.4.



**Figure 4.4 Poisson Model 2 of Annual Market Authorizations for New Orphan Drugs**

The models listed in Table 4.3 provide evidence that the US market authorized more annual new orphan drugs, on average, after and before adjusting for years and GDP growth per capita between 2004 and 2021. The US indicator remains significant and positive in models 1 through 3, robust to additions of these other variables.

The EU and US are both estimated to increase market authorizations for new orphan drugs annually, on average, after and before adjusting for GDP growth per capita and the interaction between years and region between 2004 and 2021. There is a significant positive coefficient for years in models 2 through 5.

There is moderate evidence that the US increased market authorizations for new orphan drugs at a faster rate than the EU annually, on average, after and before adjusting for annual GDP growth per capita between 2004 and 2021. The interaction between years

and region is positive and significant in models 4 and 5 however, only at the 0.1 significance level.

## CHAPTER 5

### ETHICAL CONSIDERATIONS

#### 5.1 High Prices

We cannot claim that an increase in orphan drug production and R&D spending will lead to overall social welfare improvements, as we are unsure of the marginal societal benefits of price reduction and drug production. A focus on research and development is important, but it may come with the trade-off of high prices.

For example, Imiglucerase, an enzyme replacement therapy to treat Gaucher's disease, has an annual cost that can reach \$400,000 USD per year. Eculizumab, a drug that treats paroxysmal nocturnal hemoglobinuria, can cost up to \$500,000 USD per year. Kalydeco, a cystic fibrosis treatment, exceeds \$300,000 USD per year (Jayasundara et al., 2019). These high prices are common for orphan drugs and, as discussed in section 2.2, Żelewski (2022) finds that orphan drug prices are typically higher in the US compared to the EU.

Avendano et al. (2009) finds a possible symptom of high pharmaceutical prices: individuals in the US report lower health outcomes than those in the EU. This US disadvantage is found for all wealth levels, but economically disadvantaged individuals see the largest inequity compared to their EU counterparts. With high pharmaceutical prices, more innovation may occur, but the impact may only be felt by the wealthiest individuals, if at all.

Our study should not serve as sufficient evidence that increased prices will benefit patients. High prices, health inequities, and company profits should be studied alongside

our findings. Even if R&D spending does increase with higher prices, firms may still garner excessive profits, and economically disadvantaged individuals may not receive any health benefit.

We also remain uncertain whether pharmaceutical companies would maintain their current levels of innovation if price controls were universally implemented across all markets. While EU firms may relocate to the US, attracted by the potential for higher profits, such a shift may not necessarily reflect a genuine increase in innovation.

## **5.2 Loopholes in Orphan Drug Policy**

Additionally, orphan drug policies have loopholes. For example, in March 2020, Gilead Sciences was awarded an orphan drug designation for remdesivir, a treatment for COVID-19. This occurred after the disease had been labeled a pandemic by the World Health Organization (Centers for Disease Control and Prevention, 2023). Because there were few commercial tests available before this designation request, there were sufficiently few confirmed positive cases to receive an orphan drug designation. After public backlash, Gilead asked for the designation to be revoked. However, had Gilead not done so, there would have been little precedent for the FDA to revoke the designation (Chua & Conti, 2020). Companies may unethically reap benefits reserved for rare disease medicines in order to collect excessive profits.

Firms can also obtain multiple orphan designations for the same drug and can market an orphan drug for non-rare diseases. “[O]f the 43 orphan drugs approved by the FDA whose global annual sales reached more than \$1 billion, 18 had only one orphan designation, 15 had two, and 10 had three and more” (Côté & Keating, 2012, p. 1189). Côté and Keating found that firms may exploit orphan drug policies by obtaining an

orphan designation and reaping economic benefits during the development, approval, and marketing phases. Then, firms obtain new therapeutic indications for other diseases including non-rare diseases. For example, ibuprofen, which is widely used to manage various conditions, has received an orphan drug designation to treat the rare disease, patent ductus arteriosus (Hughes-Wilson et al., 2012).

In our analysis, we find that the EU rarely awards multiple orphan drug market authorizations for the same drug, while the US does so frequently. There may be a societal benefit of authorizing the same drug for multiple rare diseases as this drug may otherwise not be used to treat diseases that may be receptive to these medicines. However, this also may be another avenue for firms to reap exorbitant profits.

In EU law, if a drug is deemed highly profitable, the market exclusivity period may be reduced to six years. However, this market exclusivity reduction has not been exercised (Bagley et al., 2019). If this provision was utilized in the EU and US, some of these loopholes may be closed, but in the status quo, firms can exploit orphan drug policies to increase profits.

### **5.3 Differences in Market Authorization Award Thresholds**

There may be differences in the threshold for orphan drug designation in the US and the EU. The EU accepts drugs that treat diseases or conditions that affect less than 5 in 10,000 people in the EU (European Medicines Agency, n.d.). The US accepts drugs that affect less than 200,000 people in the US (U.S. Food and Drug Administration, 2018). Using the US' January 2024 population of 335.9 million (U.S. Department of Commerce, 2024), the US acceptance criteria is equivalent to pharmaceuticals that treat

less than about 6 in 10,000 people in the US. These similar thresholds might indicate that the EU and US have similar definitions of what an orphan drug may be used to treat.

However, we should note the EU also requires that orphan drugs treat a condition that is debilitating or life-threatening. Additionally, for orphan drugs in the EU, there can be no currently existing satisfactory treatment for the condition, or the new treatment must offer sufficient benefits over currently existing products (Hall & Carlson, 2014). It is possible that these higher authorization thresholds increase the quality of orphan drug production. Our study focuses on the count of orphan drug market authorizations. Policymakers should also consider how the EU and US differ in quality per pharmaceutical product.

## CHAPTER 6

### CONCLUSION

Our analysis indicates that in the United States, a country with minimal price controls, there is more pharmaceutical innovation than in the European Union, a region with higher price controls. This innovation is in the form of increased R&D spending growth, market authorizations for orphan drugs, and market authorizations for new orphan drugs. However, we do not determine whether reduced price controls are the cause of increased innovation in the US.

Although an increase in pharmaceutical innovation is desirable, we must consider the tradeoffs. Without price controls, pharmaceutical prices in the US are higher than prices in the EU. If new drugs are created but are not affordable, society may not benefit from this innovation. Reduced access to prescription medicines leads to reduced health and increased health inequities, where only wealthy individuals can access the benefit of pharmaceutical innovation. There are also loopholes within orphan drug policies that allow firms to gain market exclusivity extensions and funding for products that do not solely target rare diseases.

We find moderate evidence that the US spent more on domestic R&D than the EU, between 2004 and 2021, after and before adjusting for GDP growth per capita and year. We find strong evidence that the US increased this spending at a faster rate annually than the EU, on average, after and before adjusting for GDP growth per capita. The mechanism that led to this US improvement in R&D spending is likely increased profits due to limited price controls.



Policies aiming to stimulate the focus on rare disease drugs appear to be effective in the EU and US. We find evidence that the annual number of orphan drug market authorizations and market authorizations for new orphan drugs increased in both the EU and US, on average, between 2004 and 2021, after and before adjusting for GDP growth per capita and the interaction between year and region.

We hypothesized that reduced overall profits in the EU may incentivize an increased focus on orphan drug production because of extended market exclusivity and monetary incentives to produce orphan drugs. Additionally, in the EU, a longer period of market exclusivity exists for orphan drugs than in the US.

However, we find that the US awarded more market authorizations for orphan drugs than the EU every year between 2004 and 2021, except in 2007. We find evidence that the US awarded more annual orphan drug market authorizations than the EU, on average, between 2004 and 2021, after and before adjusting for GDP growth per capita and year. There is also evidence that the US increased annual orphan drug market authorizations at a faster rate than the EU, annually, on average, after and before adjusting for GDP growth per capita.

The US awarded more orphan drug market authorizations for the same drug multiple times compared to the EU. In the US, there were 223 drugs with over one orphan drug market authorization, whereas in the EU, there were nine. It may be a societal benefit to find multiple uses for the same drug, but this may divest focus from the research of new innovative products.

Because of this authorization discrepancy between the US and EU, we analyzed the counts of orphan drugs receiving their first orphan drug market authorization. We find

that the US still awarded more market authorizations for new orphan drugs than the EU every year between 2004 and 2021, except in 2007. We find evidence that the US awarded more annual market authorizations for new orphan drugs than the EU, on average, between 2004 and 2021, after and before adjusting for GDP growth per capita and year. We also find moderate evidence that the US increased new orphan drug market authorizations at a faster rate than the EU annually on average, between 2004 and 2021, after and before adjusting for GDP growth per capita.

We find evidence of outperformance in US R&D spending growth, orphan drug market authorizations, and market authorizations for new orphan drugs. This indicates that EU orphan drug policies do not seem to outweigh the detriment of reduced R&D spending on drug production, which may be due to price controls. The US also awards an orphan drug tax credit to firms for the production of orphan drugs which also may improve US orphan drug innovation.

While we can use our models to interpret EU and US differences in the average number of annual orphan drug market authorizations between 2004 and 2021, we should be cautious if predicting future R&D spending, orphan drug market authorizations and new orphan drugs due to our small sample size and potential ceilings of drug production and spending. It is also important to note that there may be differences in the representativeness of EU and US firms' R&D spending data because not all pharmaceutical firms are members of the EFPIA or PhRMA.

There appears to be an association between price controls and reduced innovation. However, the tradeoff is high prices. Côté & Keating (2012) find that in the US, even when orphan drugs receive a market authorization, consumer costs are often not

reimbursed to patients through insurance, limiting drug access unless patients pay high out of pocket prices. This impacts economically disadvantaged individuals the most and increases health inequities that are already more pronounced in the US compared to the EU (Avendano et al., 2009). Because of the importance of R&D spending and lower consumer costs, Jayasundara et al. (2019) proposes that drug prices could potentially be regulated based partially on R&D and production costs.

Our study focuses on the counts of orphan drugs and the amount of R&D spending that occurred in the EU and US. However, this analysis may overlook differences in pharmaceutical quality. The EU has a stricter requirement that a new orphan drug offers sufficient improvements from previously existing products. This may lead to reduced numbers of orphan drugs but may increase the innovativeness of each approved drug.

## CHAPTER 7

### FUTURE RESEARCH

#### **7.1 Consumer Pharmaceutical Spending Analysis**

There is anecdotal evidence of a 2014 increase in US prices which may have catalyzed the divergence of US and EU R&D spending. In future analysis, we can quantify the association between increased prices and R&D spending. This may give us more insight into why we saw this increased US R&D growth.

#### **7.2 Country-Level Analysis**

Because orphan drug policies differ between countries in the EU, we can analyze orphan drug production on a country level. With this country-level analysis, we may be able to determine if there are specific policies shared by several countries that are associated with more or less orphan drug production. However, the impact of these policies may be difficult to isolate as price controls also differ between countries in the European Union (Gross et al., 1994).

#### **7.3 Firm-Level Analysis**

Similarly, studying spending and orphan drug production at the firm level may give us greater insight into the mechanisms that drive innovation. Shaikh et al. (2020) found a negative association between a firm's EU market share and R&D intensity. However, this result was not statistically significant when accounting for firm fixed effects including mergers, acquisitions, and number of employees. Vernon (2004) used a single dummy variable to represent a firm and found that R&D does significantly decline with the implementation of price controls.

We can investigate if our findings from analysis on the EU and US are consistent at the firm level. This would allow us to control for firm fixed effects. However, these also may be impacted by price controls and policies. Firm-level spending analysis could also be used to determine price levels that prioritize affordability and effective R&D spending.

#### **7.4 R&D Intensity**

We can apply the methods from our pharmaceutical R&D spending analysis to R&D intensity. R&D intensity measures the proportion of firm spending used on developing new drugs compared to other spending like the marketing of old drugs and stock buybacks. Shaikh et al. (2020) and Vernon (2004) represented R&D intensity as the ratio of R&D expenditure to total sales within a firm.

Golec & Vernon (2006) represented R&D intensity as R&D spending over total firm assets. They found that US firms had greater R&D intensity than EU firms every year from 1993 to 2002 except in 1995 but had lower R&D intensity compared to the EU in 2003 and 2004.

R&D intensity is a valuable metric as it measures how much a company focuses on specifically developing new drugs. The U.S. House of Representatives Committee on Oversight and Reform (2021) finds that “[f]rom 2016 to 2020, the 14 leading drug companies spent \$577 billion on stock buybacks and dividends—\$56 billion more than they spent on R&D over the same period” (p. 164). Stock buybacks are an example of how firms engage in spending outside of R&D. However, we do not argue that stock buybacks or other spending is detrimental or beneficial for society. Stock buybacks may be used as a tool to benefit top executives (Chen & Obizhaeva, 2022). However, share

repurchases are correlated with increases in R&D spending in the year following the buyback (Henning, 2018).

## **7.5 Causal Inference**

In future research, we can study the average annual difference in all new drugs and orphan drugs produced by US and EU firms. By comparing the development of all drugs to the development of orphan drugs in the EU and US, we can isolate the effect of orphan drug policies on orphan drug development from price controls and other policies.

In the US, pharmaceutical products are released under multiple FDA agencies: the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). In the US and EU, drugs are classified into categories including new molecular entities (NME), new chemical entities (NCE), new therapeutic entities (NTEs), and new active substances (NAS). To perform effective causal inference on the impact of orphan drug policies, we should acquire data on all new pharmaceutical products in the US and EU.

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## APPENDICES

### A. Data and Code Repository

All code and data can be accessed through the Git repository:

<https://github.com/benasmith1/BenaSmithThesis/tree/main>





## B. Unadjusted Models

**Table B.1 Linear Models of Annual Domestic R&D Spending (Not Adjusted for Error Structure)**

	<i>Dependent variable:</i>					
	Annual Domestic Pharmaceutical R&D Spending (Billion USD)					
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
US	7.926** (3.771)	7.926*** (2.120)	7.905*** (2.087)	-5.998* (2.960)	-5.569* (2.983)	5.530** (2.635)
Years After 2004		1.765*** (0.204)	1.809*** (0.203)	0.946*** (0.210)	0.996*** (0.215)	1.811*** (0.558)
Years After 2004 <sup>2</sup>						-0.048 (0.031)
Annual GDP Growth Rate Per Capita			0.256 (0.179)		0.140 (0.133)	0.116 (0.092)
US:Years After 2004				1.638*** (0.297)	1.586*** (0.301)	-2.595*** (0.719)
US:Years After 2004 <sup>2</sup>						0.246*** (0.040)
Intercept	38.331*** (2.667)	23.332*** (2.294)	22.136*** (2.408)	30.293*** (2.093)	29.417*** (2.250)	27.374*** (2.159)
AIC	281	240	240	218	219	185
RMSE	11	6.09	5.9	4.36	4.29	2.54
Adj R <sup>2</sup>	0.09	0.71	0.72	0.85	0.85	0.94
F Statistic	4.42	44.28	31.14	65.92	49.88	97.43
p-value	0.0431	0	0	0	0	0
<i>Note:</i>				* p<0.1; ** p<0.05; *** p<0.01		

*The standard errors listed in this table are not adjusted for residual autocorrelation.*

**Table B.2 Poisson Models of Annual Orphan Drug Market Authorizations (Not Adjusted for Error Structure)**

	<i>Dependent variable:</i>				
	Annual Number of Orphan Drug Market Authorizations				
	Model 1	Model 2	Model 3	Model 4	Model 5
US	1.344*** (0.078)	1.344*** (0.078)	1.339*** (0.078)	0.489*** (0.179)	0.507*** (0.179)
Years After 2004		0.108*** (0.007)	0.107*** (0.007)	0.046*** (0.014)	0.047*** (0.014)
Annual GDP Growth Rate Per Capita			0.009 (0.007)		0.005 (0.007)
Years After 2004:US				0.080*** (0.016)	0.078*** (0.016)
Intercept	2.433*** (0.070)	1.366*** (0.103)	1.348*** (0.103)	2.014*** (0.150)	1.987*** (0.154)
AIC	554	273	273	250	251
RMSE	20.84	8.34	8.45	7.54	7.63
Log Likelihood	-275.04	-133.55	-132.65	-121	-120.69
<i>Note:</i>	*p<0.1; ** p<0.05; *** p<0.01				

*The standard errors listed in this table are not adjusted for residual autocorrelation.*

**Table B.3 Poisson Models of Annual Market Authorizations for New Orphan Drugs  
(Not Adjusted for Error Structure)**

	<i>Dependent variable:</i>				
	Annual Number of Market Authorizations for New Orphan Drugs				
	Model 1	Model 2	Model 3	Model 4	Model 5
US	0.903*** (0.086)	0.903*** (0.086)	0.901*** (0.086)	0.667*** (0.196)	0.669*** (0.197)
Years After 2004		0.077*** (0.008)	0.077*** (0.008)	0.061*** (0.014)	0.061*** (0.014)
Annual GDP Growth Rate Per Capita			0.002 (0.008)		0.001 (0.008)
Years After 2004:US				0.023 (0.017)	0.022 (0.017)
Intercept	2.362*** (0.072)	1.629*** (0.110)	1.624*** (0.111)	1.794*** (0.162)	1.789*** (0.166)
AIC	314	215	217	216	218
RMSE	9.39	4.71	4.74	4.64	4.66
Log Likelihood	-155.15	-104.75	-104.71	-103.88	-103.87
<i>Note:</i>			* p<0.1; ** p<0.05; *** p<0.01		

*The standard errors listed in this table are not adjusted for residual autocorrelation.*

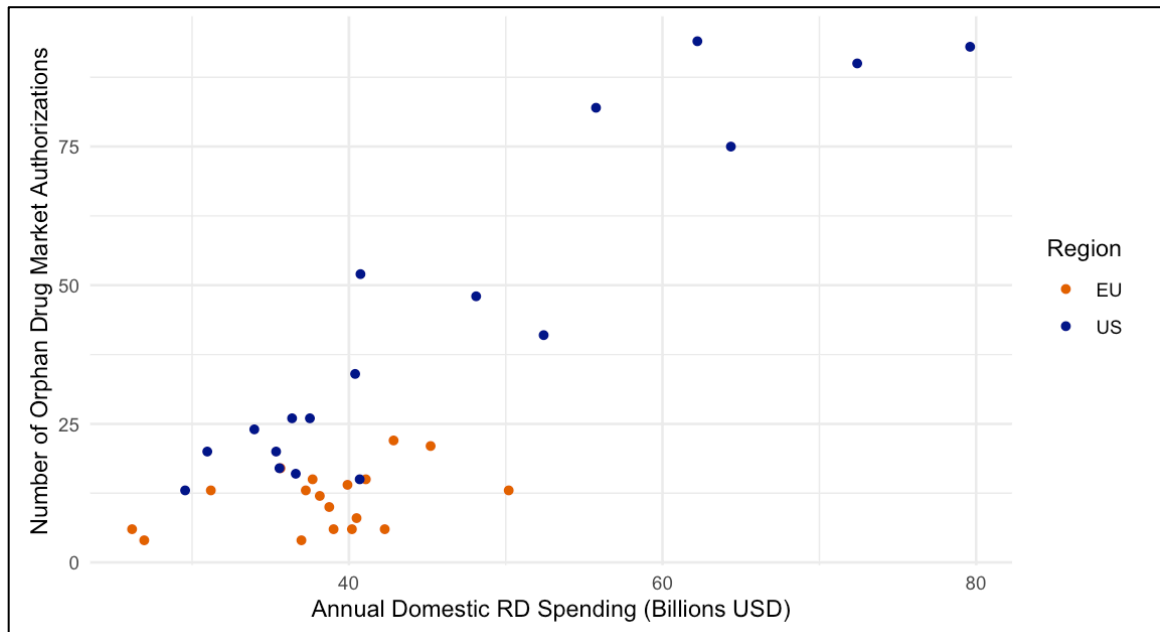
### C. Other Supplementary Materials

**Table C.1 VIFs of Predictors for Models of Annual Domestic R&D Spending**

Variable	Region	Annual GDP per capita growth rate	Years after 2004
VIF	1.00	1.02	1.02

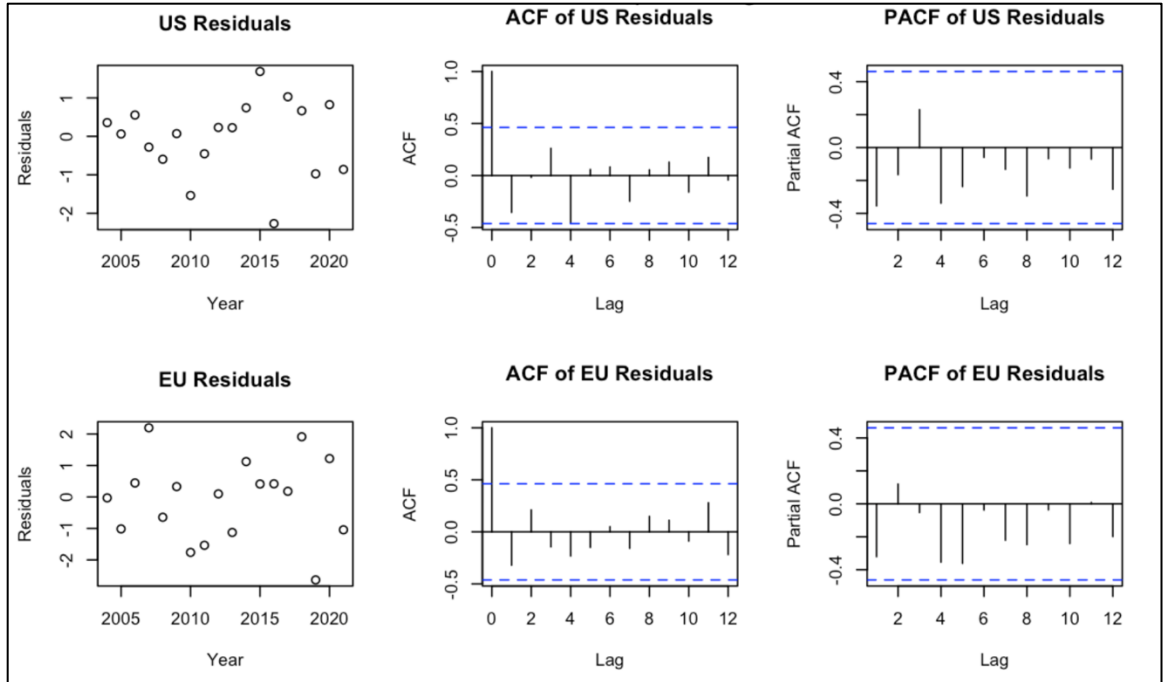
**Table C.2 VIFs of Predictors for Models of Orphan Drug Market Authorizations**

Variable	Region	Annual GDP per capita growth rate	Years after 2004	Annual Domestic R&D Spending
VIF	1.44	1.09	3.55	3.92



**Figure C.1 Annual Number of Orphan Drug Market Authorizations by Domestic R&D Spending in the US and EU**

Area and annual domestic R&D spending appear to be somewhat correlated as higher US R&D spending datapoints typically belong to the US.



**Figure C.2 Poisson Model 5 of Annual Market Authorizations for New Orphan Drugs: Residual Plots**

There looks to be potential autocorrelation in US residuals at lag 4. The coefficient of the interaction between region and years is insignificant before applying the Newey-West adjustment. After applying the adjustment, the interaction becomes significant.

## D. Selected Code

### D.1 Linear Model 6 of Annual Domestic R&D Spending

```
` `` {r}

mod.rd.6 <- lm(annual_domestic_RD_spending_bil_dollars ~
as.factor(area) + yearsafter2004 +
yearsafter2004:as.factor(area) + I(yearsafter2004^2) +
I(yearsafter2004^2):as.factor(area) +
gdp_per_capita_annual_growthrate_usd,
data=combined_rd_ma_df)

summary(mod.rd.6)

plot_linear_rd(mod.rd.6, "6")

#Estimate covariance matrix with Newey West
mod.rd.6.vcov <- vcovPL(mod.rd.6, cluster = ~
as.factor(combined_rd_ma_df$area), lag="NW1994")

#Adjust standard errors based on estimated covariance
matrix
mod.rd.nw.6 <- coeftest(mod.rd.6, vcov = mod.rd.6.vcov)
mod.rd.nw.6

confint(mod.rd.nw.6)

#Get Metrics
mod.rd.6.metrics <- get_rd_model_metrics(mod.rd.6,
"Linear")
mod.rd.6.metrics
` ``

plot_linear_rd() and get_rd_model_metrics() are functions which can be found in the
Github code repository in appendix A.
```

## D.2 Poisson Model 5 of Number of Annual Orphan Drug Market Authorizations

```
```{r}

mod.pois.od.5 <- glm(freq_orphan_drug_mas ~ as.factor(area)
+ yearsafter2004 + yearsafter2004:as.factor(area) +
gdp_per_capita_annual_growthrate_usd,
data=combined_rd_ma_df, family=poisson(link="log"))

summary(mod.pois.od.5)

plot_lin_pois_od(mod.pois.od.5, "5", "Poisson")

#Estimate covariance matrix with Newey West
mod.pois.od.5.vcov <- vcovPL(mod.pois.od.5, cluster = ~
as.factor(combined_rd_ma_df$area), lag="NW1994")

#Adjust standard errors based on estimated covariance
matrix
mod.pois.od.nw.5 <- coeftest(mod.pois.od.5, vcov =
mod.pois.od.5.vcov)
mod.pois.od.nw.5

confint(mod.pois.od.nw.5)

#Get Metrics
mod.pois.od.5.metrics <-
get_od_model_metrics(mod.pois.od.5, "Poisson")

```
```

`plot_lin_pois_od()` and `get_od_model_metrics()` are functions which can be found in the Github code repository in appendix A.