POLICIES AND PRICE CONTROLS ON THE RESEARCH AND DEVELOPMENT OF ORPHAN DRUGS IN THE US AND EU

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Master of Science in Statistics

by

Bena Smith

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| TITLE: |  | Policies and Price Controls on the Research and Development of Orphan Drugs in the US and EU |
| AUTHOR: |  | Bena Pearl Filipczak Smith |
| DATE SUBMITTED: |  | December 2024 |
| COMMITTEE CHAIR: |  | Samuel Frame, Ph.D.  Professor of Statistics |
| COMMITTEE MEMBER: |  | Eduardo Zambrano, Ph.D.  Professor of Economics |
| COMMITTEE MEMBER: |  | Trevor Ruiz, Ph.D.  Assistant Professor of Statistics |

ABSTRACT

Policies and Price Controls on the Research and Development of Orphan Drugs

in the US and EU

Bena Pearl Filipczak Smith

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

The US spends more on domestic pharmaceutical R&D than the EU every year between 2004 and 2021. **We find evidence that the US spends more on domestic pharmaceutical R&D than the EU between 2004 and 2021, on average, after adjusting for GDP growth per capita**. Prior studies have found a relationship between R&D spending and pharmaceutical development. Our study aims to identify the relationship between US and EU policies, price controls, R&D spending, and orphan drug production. 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.

We hypothesized that, with minimal price controls in the US, firms can make a high profit on other pharmaceutical products and may not be as incentivized by these orphan drug perks to create rare disease drugs. In the EU, firms may take further advantage of monetary and other orphan drug incentives.However, **we find evidence that between 2004 and 2021, the US awards more annual market authorizations for orphan drugs than the EU, on average, after adjusting for GDP growth per capita. There is evidence that the US increases the rate of doing so faster than the EU. We also estimate that the US awards more annual market authorizations for new orphan drugs than the EU, on average, between 2004 and 2021, after adjusting for GDP growth per capita**. **We do not find evidence that the US increases annual average new orphan drug market authorizations faster than the EU.** Orphan drug policies do not seem to change firm behavior much from overall R&D spending.

**Lastly, we find that an increase in R&D spending in the US is associated with more orphan drug market authorizations and new orphan drugs compared to the EU, on average, between 2004 and 2021, after adjusting for GDP growth per capita.** This may indicate that firms in the US allocate more R&D spending to the production of orphan drugs than firms in the EU. It also may be cheaper to produce new orphan drugs in the US compared to the EU, or the US may produce these drugs more efficiently. Our study does not deduce the cause of these differences however, both mechanisms point to orphan drug policies in the US being more effective at stimulating orphan drug production.

Our results point to an association between EU price controls and policies and reduced pharmaceutical innovation. This is seen in the form of less R&D spending, orphan drug market authorizations, and new orphan drugs compared to in the US. However, we must also consider that EU consumers benefit from lower average pharmaceutical prices compared to the US.

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, para. 1). The relationship between price controls and research and development (R&D) spending has been studied extensively however, most of these studies concluded before 2007. We aimed to first investigate if this relationship continues to exist in recent years.

Many studies have examined the link between price controls on research and development spending and the number of medicines produced. Few studies have focused on the relationship between price controls and the development and sale of orphan drugs, pharmaceutical products that target rare diseases (Orphanet, *About Orphan Drugs*, n.d.).

In our analysis, we investigate if the negative relationship between price controls and R&D spending has continued into recent years and if this trend is the same for orphan drugs.

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). Our analysis aims to build on this research that concluded in 2007.

The United States (US) and European Union (EU) aim to incentivize the production of orphan drugs through the 1983 US Orphan Drug Act (National Organization for Rare Disorders, n.d.) and the 1999 Regulation (EC) No 141/2000 of the European Parliament and of the Council (Publications Office of the European Union, 2000), respectively. Orphan drug studies have focused primarily on prices of orphan drugs and costs of development. Our study aims to investigate how differing policies in the United States and European Union are associated with the number of orphan drugs authorized for sale.

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

Vernon (2004) explained that current cash flows and future profit expectations spur pharmaceutical R&D. In the United States, pharmaceutical prices are largely unregulated (Vernon, 2004, p. 3). In all other major pharmaceutical markets (Abbott & Vernon, 2005, para. 1), specifically in the European Union, prices are regulated through “product-by-product price controls, limits on insurers' reimbursement levels or profit controls” (Gross, Ratner, Perez & Glavin, 1994, p. 130).

Thus, companies that sell more pharmaceutical products outside the US market face more price regulations. This reduces company profits as 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.

Through studies of firm-level R&D, Golec & Vernon (2006) found that in 1986, EU pharmaceutical R&D spending was 24 percent higher than US spending but by 2004, US spending exceeded EU spending by about 15 percent. Between 1993 to 2004, US R&D spending was greater than EU R&D spending every year. (Golec & Vernon, 2006, p. 2).

Shaikh, Del Giudice, & Kourouklis (2020) used a pharmaceutical company’s proportion of market share in the European Union to their market share in the United States to represent their 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) highlight the complication of pharmaceutical spending analysis that firms report only total R&D spending rather than domestic and international spending separately. 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, p. 18). 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), which report total R&D and domestic R&D for their members by year. We used this data to perform our analysis of domestic R&D spending in the EU and US. Most large pharmaceutical companies are members of the PhRMA and EFPIA (Pharmaceutical Research and Manufacturers of America (PhRMA), *About*, n.d., para. 5) (European Federation of Pharmaceutical Industries and Associations (EFPIA), *About Us*, n.d., para. 1). Because these trade groups do not include all pharmaceutical companies in the US and EU, differences in these organizations’ representations of the EU and US pharmaceutical markets may impact our conclusions when comparing their member’s R&D spending.

Increasing R&D spending is impactful as the price to develop new pharmaceuticals is high. The R&D cost of developing a new drug is estimated to be between $314 million and $4.46 billion, depending on its therapeutic area, the analyzed data, and modeling assumptions (Sertkaya et al 2024, p. 2).

**2.2 Orphan Drugs**

**2.2.1 Orphan Drug Studies**

Orphan drugs are medicines that target rare diseases. 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 (FDA, n.d., para 2). 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., para. 1).

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 (ScienceDirect Topics, n.d., para. 1). When these drugs are sold, there is a thinner market to recoup development costs because of the smaller number of patients with these diseases. Thus, firms charge higher prices for these products. Simoens (2011) studied the prices of pharmaceutical products in Belgium. They found a negative association between the cost of an orphan drug and the prevalence of a disease. Their model is as follows.

,

" (Simoens, 2011, p. 3).

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 EU countries. The average price ratio was 1.64 (Żelewski et al., 2022, p. 1).

Both the United States and the European Union aim to stimulate the production of orphan drugs through policy. Other countries including Japan, China, South Korea, Taiwan, and Australia also have policies aiming to spur the development of rare disease drugs (Song et al., 2012).

In the European Union, drugs with an orphan designation are allowed a 10-year market exclusivity period plus 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 pediatric exclusivity for qualified 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 (Hall & Carlson, 2014, p. 2).

While they may be more difficult to develop, orphan drug policies and development practices can make orphan drugs 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 total R&D cost required per market success for an approved orphan drug was found to be $166 million (2013 USD) compared to $291 million per non-orphan drug (Jayasundara et al., 2019, p. 1). Tax credits can account for some of this difference, as well as the use of small sample sizes in clinical trials (Côté & Keating, 2012)

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 the clinical trial cost (Austin and Hayford, 2021, p. 37).

In the European Union, 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, p. 4). More benefits are listed in Horgan et al. and include reduced fees, reimbursements, faster pricing periods, and dedicated funds for orphan drug development.

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

The incentives provided to incentivize the production of orphan drugs may result in a different R&D trend compared to that of all pharmaceutical products.

**2.2.2 Orphan Drug Policies**

The following is a timeline of selected notable policies in the US and EU surrounding orphan drug production. This table is not an exhaustive list of all orphan drug policies and does not contain more general pharmaceutical policies that may impact orphan drug production.

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

|  |  |  |
| --- | --- | --- |
| **Year** | **EU Policies** | **US Policies** |
| 1983 |  | **Orphan Drug Act**  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 and Wadhwa, 2021, p. 1). |
| 1985-1990 |  | **1985 and 1990 amendments of the Orphan Drug Act**  Biologics, medical devices and medical foods are included in the definition of an orphan product (Orphanet, *Orphan Drugs in the United States of America*, n.d., para 7). |
| 1992 |  | **1992 amendment of the Orphan Drug Act**  If an orphan drug is similar to one currently authorized for the same disease, a firm must demonstrate the clinical superiority of the new drug to receive an orphan designation. Additionally, more than one sponsor can receive an orphan designation for the same drug. Market exclusivity is given to the first firm to file an NDA. 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, *Orphan Drugs in the United States of America*, n.d., para 7). |
| 2000 | **Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products**  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). |  |
| 2006 | **Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use**  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, para. 29). |  |
| 2017 |  | **2017 Tax Act**  This act reduced tax credits awarded to orphan drugs from 50 percent of clinical trial costs to 25 percent (Austin and Hayford, 2021, p. 37) (U.S. Government Publishing Office, p. 131). |

**2.3 Ethical and Structural Considerations**

Over the course of our study, we must be aware of the ethical implications of our findings. 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, might cost as much as $400,000 USD per year for an adult patient. A drug that treats paroxysmal nocturnal hemoglobinuria, eculizumab, can cost up to US $500,000 per patient per year. Kalydeco, used to treat a subpopulation of cystic fibrosis patients, exceeds $300,000 USD per year per patient” (Jayasundara et al., 2019, p. 1). These high prices are common for orphan drugs and, as discussed in section 2.2.1, Żelewski finds that orphan drug prices are typically higher in the US compared to the EU. We must consider this tradeoff during our analysis. We cannot claim that an increase in orphan drug production will lead to overall social welfare improvements as we are unsure of the marginal societal benefits of price reduction and drug production.

Additionally, orphan drug policies have loopholes. For example, in March 2020, Gilead Science was awarded an orphan drug designation for remdesivir, a treatment for COVID-19. This occurred after the disease had been labeled as 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 significantly few positive confirmed cases to receive an orphan drug designation. After public backlash, Gilead asked for the designation to be revoked but had Gilead not done so, there would have been little precedent for the FDA to revoke the designation (Chua & Conti, 2020, para. 2). Companies may unethically reap benefits reserved for rare disease medicines in order to collect excessive profits.

Firms can 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 often 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. (Côté & Keating, 2012, p. 1189) We investigate the difference in the EU and US’ designations for the same drugs in section 4.3 and find that the EU rarely awards multiple orphan market authorizations for the same orphan 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, but this also may be another avenue for firms to reap excessive 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, p. 132).  If this provision was utilized in the EU and US, some of these loopholes may be closed, but in the status quo, firms often exploit orphan drug policies to increase profits.

Another structural consideration is that there may be differences in the threshold for orphan drug designation in the US and EU. The EU accepts drugs that treat diseases or conditions that affect less than 5 in 10,000 people in the EU and the US accepts drugs that affect less than 200,000 people in the US. Using the US’ January 2024 population of 335.9 million (U.S. Department of Commerce, Jan. 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 indicate that the US and EU have similar definitions of what an orphan drug may be used to treat.

Chapter 3

METHODS

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

We first investigated the differences in US and EU pharmaceutical R&D spending from 2004 to 2021. In our models, 2004 is coded as year 0. Golec and Vernon’s similar 2006 study of the 1986 to 2004 time period has a one year longer study period than our analysis. We performed our analysis of R&D spending using annual EFPIA and PhRMA member data (European Federation of Pharmaceutical Industries and Associations (EFPIA), *The Pharmaceutical Industry in Figures*, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2014, 2015, 2016 2017, 2018, 2019, 2020, 2021, 2022, 2023) (Pharmaceutical Research and Manufacturers of America (PhRMA), *2022 PhRMA Annual Membership Survey,* 2022). We modeled 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). European data was converted from euros to US dollars using the annual average closing exchange rate (Macrotrends, *Euro Dollar Exchange Rate (EUR USD) - Historical Chart*, 2024) and spending amounts are measured in billions of US dollars. 2011 EFPIA spending was not found, so it was imputed by the average of EFPIA spending in 2010 and 2012 in euros. It is necessary to impute this value, so we have consistent measurements over time as this is an assumption of the Newey-West adjustment for time-dependent, autocorrelated data discussed in section 3.4.2.

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

A graph showing the growth of the us dollar

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

*EU Data for Annual Domestic R&D Spending in 2011 was imputed by averaging EU spending in 2010 and 2012 in euros because this data was not available. EU data was converted from euros to US dollars based on the annual average closing exchange rate.*

Golec and Vernon found that EU domestic R&D spending exceeded that of the US from 1986 to 1997, and US spending exceeded EU spending from 1998 to 2004 (Golec and Vernon, 2006, p. 9). We can see visually that this trend has continued as the US outspends the EU in domestic pharmaceutical R&D spending every year from 2004 to 2021.

We analyzed this difference in R&D spending in the US and EU by performing five linear regressions of R&D spending with different combinations of explanatory variables: years after 2004, area (US and EU), annual GDP growth rate per capita, polynomial transforms of the years after 2004 variable and interactions between these variables. Annual GDP growth rate per capita was 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). Polynomial transforms of the years after 2004 variable were included to capture the visual curvature in R&D spending.

In R, we used the lm() function in the stats package to estimate our model coefficients. The code for our full model of annual domestic R&D spending in R can be found in appendix E.1.

We tested models with different combinations of these variables to analyze if these predictors are robust to variable additions. We chose best models 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 selection process was 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 not obvious if the number of market authorizations will follow the same trend as overall domestic R&D. The total number of market authorizations for orphan drugs to be sold in the US and EU were counted by year. Market authorizations in the EU were obtained from Orphanet (Orphanet, *Lists of Medicinal Products for Rare Diseases in Europe,* 2021) and market authorizations in the US were obtained from the FDA (U.S. Food and Drug Administration (FDA), *Search Orphan Drug Designations and Approvals*, 2024).

First, we visualize the annual number of market authorizations of orphan drugs for sale in the EU and US. A graph showing the number of drug market

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

**EU and US**

The US awards more market authorizations for orphan drugs every year except for 2007. The US looks to increase annual market authorizations at a faster rate than the EU.

We perform six linear regressions of the annual number of market authorizations (MAs) for orphan drugs with different combinations of explanatory variables: years after 2004, area (US/ EU), R&D spending, annual GDP growth rate per capita and interactions between these variables.

For these linear models, we use the same modeling process as our R&D spending models, as discussed in section 3.1. The code for our full linear model of annual orphan drug market authorizations can be found in appendix E.2.

Due to the count nature of the data (count of orphan drug market authorizations), a Poisson generalized linear model may be a better fit than our linear models. Poisson models typically represent counts well as they do not allow for a negative response. They also allow for a curved, non-linear relationship between explanatory and response variables because a log link function is used (Jabeen, 2019).

We use the glm() function in the stats package in R with family=poisson(link="log") to estimate our model coefficients. The code for our full Poisson generalized linear model of annual orphan drug market authorizations can be found in appendix E.3.

We chose best Poisson models using the models’ AIC. Because AIC is calculated based on the log likelihood of the model and Poisson generalized linear models and linear models have differing log likelihoods, it is disputed whether these models can be compared using AIC. Many use AIC to compare models that are fitted with maximum likelihood on the same data (Rdocumentation). The lm() and glm() R functions use maximum likelihood estimation (Franke). However, some literature finds that models must be nested for AIC to be used (Ripley, 2004).

Thus, we also compare the root mean squared error (RMSE) of Poisson and linear models to get a measurement of how far the observed data is from our model. RMSE does not penalize more complex models so we should use it only to compare Poisson and linear models with the same predictors. This model selection procedure is also carried out when modeling new orphan drugs, as discussed in section 3.3.

* 1. **Market Authorizations for New Orphan Drugs**

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

**Table 3.1 US Market Authorization Frequencies for Orphan Drugs with Over 5 Market Authorizations**

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

**Table 3.2 EU Market Authorization Frequencies for Orphan Drugs with Over 1 Market Authorization**

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Because of this discrepancy, we want to investigate the factors influencing the number of market authorizations for new orphan drugs each year.

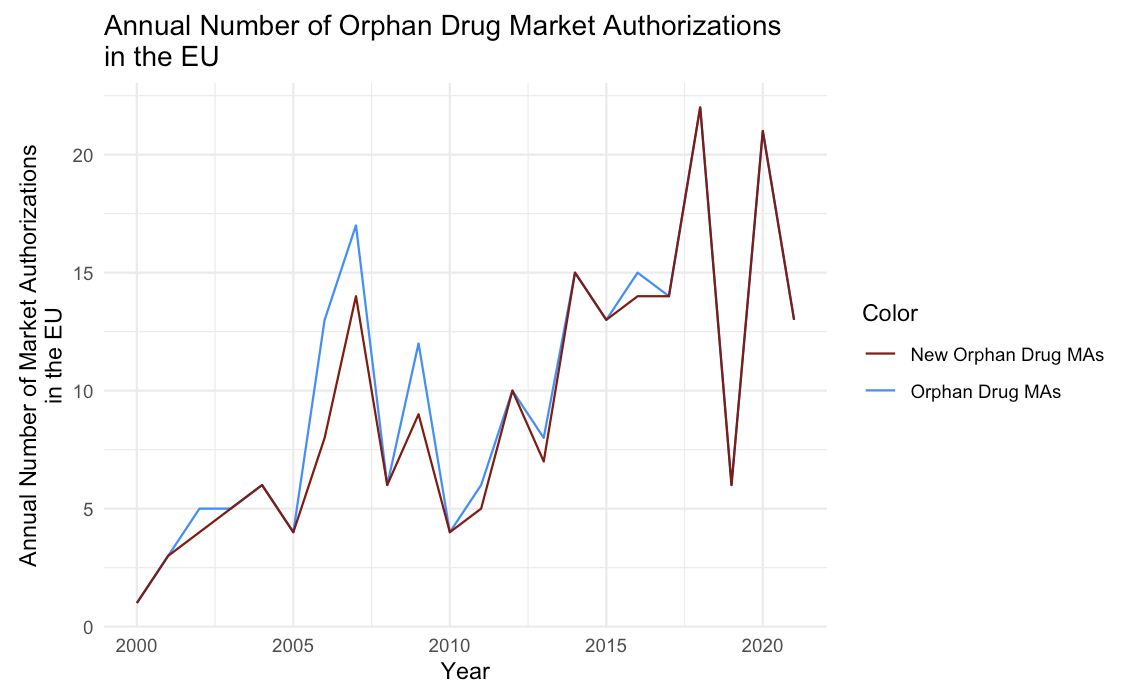
The following figures show the annual counts of all market authorizations compared to the annual counts of market authorizations for new orphan drugs in the US (Figure 3.3) and the EU (Figure 3.4)

A graph showing the number of drug market authorities

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

We can see the visual divergence between the trend of orphan drug market authorizations overall and market authorizations for new orphan drugs in the US.



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

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

Below is a graph of market authorizations for new orphan drugs that have not had a market authorization in the past in the US and EU.

A graph of a number of drugs

Description automatically generated

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

The US still awards more annual new orphan drug market authorizations than the EU in every year, except in 2007. However, the slopes between the US and EU in figure 3.5 look closer than the slopes between the US and EU of all orphan drug market authorizations in figure 3.2.

We followed the same procedure as discussed in section 3.2 of modeling using linear and Poisson generalized linear models. Our response variable is now annual number of market authorizations for new orphan drugs. The code for our full linear model of market authorizations for new orphan drugs can be found in appendix E.4. The code for our full Poisson generalized linear model of market authorizations for new orphan drugs can be found in appendix E.5.

* 1. **Model Assumptions**

After performing these regressions, we must check the assumptions of linear regression to ensure our conclusions are accurate. We can do so by analyzing the residuals of our models. Because this is panel data, we perform residual analysis on EU and US data separately.

**3.4.1 Constant Variance and Normality of Residuals and Collinearity of Predictors**

With residual plots, we can confirm linearity and constant variance of residuals. QQ plots are used to evaluate if residuals are normally distributed at each combination of predictor values. To ensure that there is minimal collinearity between predictor variables, we calculate variance inflation factors (VIFs). Variance inflation factors are calculated for models with all predictors but no interactions or polynomial terms because interactions and higher-order terms of a predictor will be correlated with that predictor.

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

Because we are working with time series data, the assumption of independent model residuals is likely violated as observations may be time dependent. The traditional ordinary least squares estimate of coefficient standard errors assumes that residuals have a covariance of zero. If residuals are correlated with one another, the covariance of errors is greater than zero. We can view the autocorrelation of residuals with autocorrelation function (ACF) and partial autocorrelation function (PACF) plots. If there is autocorrelation at any lag greater than lag zero, there is evidence that the assumption of residual independence has been violated.

Regardless of the appearance of these plots, we calculated the Newey-West estimator for the residuals of each model. This method estimates the autocorrelation between residuals with the assumption that the covariance between observations decreases as the time between observations increases. Standard errors of our coefficient estimates are calculated accounting for existing 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, p. 3). The Newey-West estimator is also easily applied to panel data (Zeileis and Lumley). Because we are studying US and EU spending, we are modeling two separate time series, or panels. Thus, the covariance of observations must be calculated separately for each panel. Alternatively, we could explicitly model the autoregressive and moving average (ARMA) nature of our time series however, “high order ARMA(p, q) processes are difficult to identify and estimate in practice and are rarely used in the analysis of financial data” (Zivot and Wang, 2006, p. 76). Estimating ARMA models is more complex process than adjusting standard errors, especially when data is paneled (Li et al., 2021).

Before applying the Newey-West estimator, we investigate residual plots to ensure that our residuals are stationary. That is, the correlation of residuals does “not depend on the time at which the series is observed” (Hyndman and Athanasopoulos, 2018, para. 1). This means that we can estimate the correlation structure of our data on a basis of only the distance between observations. To ensure this, residuals should not display a trend or cyclic nature (para. 1). After standard errors are corrected, we can interpret our model coefficients alongside their corrected p-values.

We use the vcovPL() function in the R sandwich package to apply Newey-West adjustments to our panel data (Zeileis and Lumley). All models in our analysis are adjusted using this function.

Chapter 4

ANALYSIS

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

The following table shows five linear regressions estimating 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 five 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 in appendix table B.1.

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

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Variance inflation factors are computed for model 3, the model with all predictors and no interactions or polynomials. All main effects show no evidence of collinearity. These VIFs are listed in appendix table D.1. Our best model on a basis of AIC is model 6 which is plotted below in figure 4.1.

A graph of a number of people

Description automatically generated with medium confidence

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

The polynomial term for years after 2004, included as a main effect and in an interaction with area, best captures the curvature in domestic R&D spending over time. The other models do not capture this curvature well. The second-best model on a basis of AIC is model 4 which is pictured below in figure 4.2. Model 4 does not contain this polynomial term.

**A graph with blue and orange dots

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**Figure 4.2 Linear Model 4 of Annual Domestic R&D Spending**

There looks to be model misspecification in model 4 due to the unrepresented curvature in our residuals, especially for US data. Thus, the regression assumption of residual linearity is violated. Residual panels can be found in appendix C.1 and C.2. The p-values are likely inaccurately adjusted when applying the Newey-West method due to nonstationary. However, conclusions of model 4 align with the more complex model 6.

The models listed in Table 4.1 provide evidence that the US spends more on annual pharmaceutical research and development, on average, after and before adjusting for GDP growth per capita between 2004 to 2021. The US coefficient remains significant and positive in every model, robust to additions of other variables.

The US and EU are both estimated to increase spending on R&D annually, on average, after and before adjusting for GDP growth per capita. There is a positive and significant coefficient for years after 2004 in every model except model 6. The years after 2004 coefficient becomes insignificant in model 6 when the higher order term, years after 2004 squared, is added to the model. This higher-order term is positive and significant in model 6, indicating the same conclusion, that the US and EU are both estimated to increase R&D spending on average annually after adjusting for GDP growth per capita.

There is evidence that the US increases annual R&D spending at a significantly higher pace, on average, after adjusting for annual GDP growth per capita. The coefficient estimate of the interaction between years after 2004 and area is positive and significant in models 4 and 5. This coefficient becomes negative when the higher-order term, years after 2004 squared interacted with the US, is added in model 6. This higher order term is positive and significant in model 6, indicating that there is still evidence that the US increases annual R&D spending at a faster rate than EU spending after adjusting for GDP growth per capita.

R&D spending directly leads to the creation of new drugs. Sertkaya et al. (2024) estimates that the R&D cost for developing a new drug ranges from $314 million to $4.46 billion.

Although model 6 fit our model best, it is less interpretable than the other models because of polynomial year terms. Without accounting for the differing slopes of R&D spending in the US and EU, we can look at model 3 which only estimates the overall slope of average R&D spending in the US and EU from 2004 to 2021 and the average difference between annual US and EU R&D spending. The coefficient for the US indicator in model 3 has a confidence interval of (14.71, 27.83). With 95% confidence, our model estimates that from 2004 to 2021, the US spent between 14.71 and 27.83 billion US dollars more annually than the EU on domestic pharmaceutical R&D on average, after adjusting for GDP growth per capita and year. Using Sertkaya’s estimates of R&D cost per drug, this is a potential loss of between 3.3 and 88.6 new drugs annually, on average, in the EU, compared to the US from 2004 to 2021.

Model 4 does still capture the overall increasing trend of domestic R&D spending in the US and EU. The confidence interval for the interaction between US and years after 2004 in model 4 was (0.75, 2.06). With 95% confidence, our model estimates that the US increases R&D spending between 0.75 and 2.06 billion US dollars more than the EU annually, on average between 2004 and 2021, after adjusting for GDP growth rate per capita. This is a potential loss of between 0.17 to 6.6 new drugs in average annual new drug growth compared to the last year, in the EU, compared to the US from 2004 to 2021.

**4.2 Orphan Drug Market Authorizations**

**4.2.1 Linear Models of Orphan Drug Market Authorizations**

Next, we modeled the number of market authorizations for orphan drugs with linear models with different combinations of the predictors; area (US/EU), years after 2004, annual GDP growth rate per capita, annual domestic R&D spending, and interactions between these predictors. The standard errors of the model coefficients in table 4.2 have been adjusted using the Newey-West estimator. Unadjusted models are in appendix table B.2.

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

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Variance inflation factors are computed for model 2, the model with all predictors and no interactions. Area, years after 2004 and annual domestic R&D spending have VIFs that indicate multicollinearity. These VIFs are listed in appendix table D.2. When calculating the predictors’ correlation matrix, as shown in appendix table D.3, annual domestic R&D spending has a correlation of about 0.63 with years. We confirmed that this linear relationship between years and R&D spending exists in section 4.1, so this is not surprising. There is also evidence of collinearity as annual domestic R&D spending, years after 2004, and, the years after 2004 and area interaction become non-significant predictors when simultaneously added in model 6. We lose predictive information when correlated predictors are adjusted for one another. Because of this collinearity, we focus on model 3 and 4 which investigate the trend of orphan drug market authorizations over time in a separate model from the relationship between domestic R&D spending and orphan drug market authorizations. Models 3 and 4 are pictured below in figures 4.3 and 4.4.

A graph of a graph showing the number of drugs

Description automatically generated with medium confidence

**Figure 4.3 Linear Model 3 of Annual Orphan Drug Market Authorizations**

A graph showing the growth of drug market

Description automatically generated

**Figure 4.4 Linear Model 4 of Annual Orphan Drug Market Authorizations**

Residual panels are shown in appendix C.3 and C.4 and look to have roughly constant variance, linearity, and normality. There looks to be some evidence of autocorrelation in EU residuals, so a Newey-West adjustment is necessary.

Model 1 shows a positive and significant US indicator, which becomes negative and significant when annual domestic R&D spending, years after 2004, GDP growth per capita and interactions are added in models 4 and 5. This is the predicted number of how many fewer market authorizations the US would have in 2004 compared to the EU if annual GDP growth per capita was zero. However, the US has more market authorizations than the EU every year from 2004 to 2021. Because we are using linear models, when slopes are better captured by adding years and R&D spending, the intercept is likely not able to be captured accurately. We try Poisson generalized linear models in section 4.2.2 to account for this potential limitation.

The positive and significant interaction between years after 2004 and US in model 3 shows evidence that the US increases the number of annual market authorizations at a faster rate, on average compared to the EU between 2004 and 2021, after adjusting for GDP growth per capita. This coefficient is not robust to the addition of R&D spending. This is likely due to collinearity between these predictors.

The coefficient of annual domestic R&D spending is also positive and significant, indicating evidence that an increase in annual domestic R&D spending is associated with more annual orphan drug market authorizations in the EU and US, on average, between 2004 and 2021, after adjusting for GDP growth per capita.

There is evidence that an increase in domestic R&D spending is associated with a greater number of annual market authorizations for orphan drugs in the US than the EU between 2004 and 2021, on average, after adjusting for annual GDP growth rate per capita. The interaction between annual domestic R&D spending and the US in Model 4 is positive and significant. This coefficient is not robust to the addition of years after 2004, likely because of collinearity between these predictors. Our Poisson model in 4.2.2 finds coefficient estimate of the R&D spending and US interaction to be nonsignificant so we should be cautious about this conclusion. However, the RMSE of the linear model is less than the Poisson model so we will prefer the conclusion that this estimate is significant.

The increase in R&D spending being associated with more average market authorizations in the US compared to the EU may occur because the US awards more market authorizations for the same drug than the EU, as discussed in section 3.1. It is likely cheaper to market authorize drugs that have been already developed for a new disease rather than develop a completely new drug.

**4.2.2 Poisson Models of Orphan Drug Market Authorizations**

We next use Poisson generalized linear models to better account for potential linear modeling inaccuracies including curvature and negative intercepts. Models are shown in table 4.3 with Newey-West adjusted standard errors. Unadjusted models are displayed in appendix table B.3.

**Table 4.3 Newey-West Adjusted Poisson Models of Orphan Drug Market Authorizations**

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As discussed in 4.2.1, because of correlated variables, year and R&D spending, we will focus on models 3 and 4 which model these variables separately. Models 3 and 4 are pictured below in figures 4.5 and 4.6.

A graph of a graph showing the number of drug manufacturers

Description automatically generated with medium confidence

**Figure 4.5 Poisson Model 3 of Annual Orphan Drug Market Authorizations - Residual Plots**

**A graph showing the number of drug companies

Description automatically generated**

**Figure 4.6 Poisson Model 4 of Annual Orphan Drug Market Authorizations**

Residual panels of models 3 and 4 are displayed in appendix C.7 and C.8 and look to have roughly constant variance, linearity, and normality except for potential non-linearity in US residuals between 2014 to 2018. There is not apparent evidence of residual autocorrelation however, we still apply a Newey-West estimator adjustment to standard errors.

The coefficient for the US indicator is positive and significant in models 1, 2 and 3 showing evidence that the US market authorizes more orphan drugs on average compared to the EU, after and before adjusting for GDP per capita. This effect is not significant after adjusting for the interaction between the US and R&D spending.

The interaction between years and the US in model 3 is positive and significant, showing evidence that the US increases the number of annual market authorizations at a faster rate, on average, compared to the EU after adjusting for GDP growth per capita. Both linear model 3 and Poisson model 3 lead us to the same conclusion that the US increases the number of annual orphan drug market authorizations at a faster rate than the EU, on average, from 2004 to 2021, after adjusting for GDP growth per capita. This coefficient remains positive and significant in model 5 when the interaction between US and R&D spending is added, implying strong evidence that this association exists.

These Poisson models do not provide evidence that an increase in R&D spending is associated with a higher number of market authorizations for orphan drugs in the US compared to the EU, as indicated by the insignificant interaction between annual R&D spending and the US in model 4. This is a different conclusion from our linear model, which showed evidence of US R&D spending being associated with more market authorizations than the EU, on average, after adjusting for GDP growth per capita. Linear model 4 has a lower RMSE than Poisson model 4, so the conclusions of the linear model will be preferred over this Poisson model. We conclude that there is evidence of a greater increase in average annual orphan drug market authorizations associated with an increase in R&D spending in the US compared to the EU, after adjusting for GDP growth per capita between 2004 and 2021.

**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 will perform the same modeling for market authorizations for new orphan drugs.

**4.3.1 Linear Models of Market Authorizations for New Orphan Drugs**

The following table displays five linear models of 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 in appendix table B.4.

**Table 4.4 Newey-West Adjusted Linear Models of Market Authorizations for New Orphan Drugs**

**A table with numbers and a number of text

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As discussed in 4.2.1, because of correlated variables, year and R&D spending, we will focus on model 3 and 4 which model these variables separately. Models 3 and 4 are pictured below in figures 4.7 and 4.8.

**A graph of a number of drugs

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**Figure 4.7 Linear Model 3 of Annual Market Authorizations for New Orphan Drugs**

**A graph showing the number of drugs

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**Figure 4.8 Linear Model 4 of Annual Market Authorizations for New Orphan Drugs**

The residuals of models 3 and 4 look to have roughly constant variance, linearity, and normality except for potential non-linearity in US residuals between 2014 to 2018. Residual panels are shown in appendix C.7 and C.8. There looks to be some evidence of autocorrelation in the EU residuals, so a Newey-West adjustment is necessary.

There is evidence that the US produces more annual new orphan drugs than the EU in model 1 on average, evidenced by the positive and significant coefficient for the US indicator. This becomes insignificant in the other models when years after 2004, R&D spending, GDP growth per capita and interactions with area are added to the model. The US market authorizes more new orphan drugs than the EU every year between 2004 and 2021 so this intercept change when adding predictor variables that better account for the slope may be due to the linear quality of our model. We will fit Poisson models in section 4.3.2 to attempt to better account for curvature that exists in our data.

The positive and significant interaction between year and US in model 3 shows evidence that the US increases the number of annual market authorizations for new orphan drugs at a faster rate, on average, compared to the EU between 2004 and 2021, after adjusting for GDP growth per capita. However, this claim is disputed in 4.32 when modeling with a Poisson model with lower RMSE.

There is evidence that an increase in domestic R&D spending is associated with a greater number of annual market authorizations for new orphan drugs in the US than the EU between 2004 and 2021, on average, after adjusting for annual GDP growth rate per capita. This is evidenced by the positive and significant interaction between annual domestic R&D spending and the US in Model 4. This contrasts with our Poisson model in section 4.3.2 which finds the opposite, that in the EU, an increase in R&D spending is associated with a greater number of market authorizations for new orphan drugs after adjusting for GDP growth per capita. Our linear model has a lower RMSE so we will prefer the conclusion that US R&D spending is associated with more new orphan drugs, on average however, we should be cautious when making policy decisions from this finding.

The greater increase in new orphan drugs associated with an increase in R&D in the US compared to the EU indicates that it may be cheaper in the US to produce new orphan drugs. The US may also allocate proportionally more R&D spending to orphan drug production than the EU. Protocol assistance, national grants and reduced fees exist in both the US and the EU (Hall & Carlson, 2014), but these results show that these policies may be more effective in the US at reducing the cost of producing a new orphan drug or incentivizing R&D focus on orphan drugs.

**4.3.2 Poisson Models of Market Authorizations for New Orphan Drugs**

We will again also model this data using Poisson generalized linear models due to its count nature to investigate if Poisson models are a better fit. The following table displays five linear models of 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 in appendix table B.5.

**Table 4.5 Newey-West Adjusted Poisson Models of Market Authorizations for New Orphan Drugs**

A table of numbers and text

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As discussed in 4.2.1, because of correlated variables, year and R&D spending, we will focus on model 3 and 4 which model these variables separately. Models 3 and 4 are pictured below.

A graph showing the number of drugs

Description automatically generated

**Figure 4.9 Poisson Model 3 of Annual Market Authorizations for New Orphan Drugs**

**A graph showing the number of drugs

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**Figure 4.10 Poisson Model 4 of Annual Market Authorizations for New Orphan Drugs**

The residuals of models 3 and 4 look to have roughly constant variance, linearity, and normality except for potential non-linearity in US residuals between 2011 to 2018. Residual panels are shown in appendix C.9 and C.10. There is not apparent evidence of residual autocorrelation however, we still apply a Newey-West adjustment to standard errors.

The US indicator is positive and significant for Poisson models 1 through 4 of new orphan drug market authorizations, implying that there is evidence that the US awards more market authorizations for new orphan drugs, on average after adjusting for year, GDP growth per capita, and domestic R&D spending. This intercept is presumed to be insignificant in model 5 due to collinearity with interaction terms including the US variable.

There is not evidence in model 3 that the US increases the number of annual market authorizations for new orphan drugs at a faster rate, on average compared to the EU after adjusting for GDP growth per capita. This is evidenced by the insignificant interaction between years and the US indicator. This is a different conclusion from linear model 3, where this coefficient was positive and significant. The RMSE of Poisson model 3 is less than the RMSE of linear model 3 so this Poisson model fits our observed data better than the linear model. Thus, we will prefer the conclusions of our Poisson model, that there is not evidence that the US increases the number of annual market authorizations for new orphan drugs at a faster rate, on average compared to the EU after adjusting for GDP growth per capita.

There is evidence that an increase in R&D spending is associated with a lower number of market authorizations for new orphan drugs in the US compared to the EU. The interaction between annual R&D spending and the US is negative and significant in Poisson model 4. This is an opposing conclusion to our linear model which showed evidence of a positive relationship between US spending and market authorizations for new orphan drugs. Linear model 4 has a lower RMSE than Poisson model 4, so the conclusions of linear model 4 will be preferred over this Poisson model and we will conclude that there is evidence of a further average increase in new orphan drug market authorizations when R&D spending increases in the US compared to the EU.

Our R&D spending data is from the EFPIA and PhRMA, trade groups including only major pharmaceutical firms. Our orphan drug data is from the FDA and Orphanet and includes all orphan drug market authorizations from all pharmaceutical firms. Thus, we should not interpret the coefficient for R&D spending’s association with number of orphan drugs as the cost per new orphan drug or orphan drug market authorization.

CHAPTER 5

CONCLUSION

We estimate that in the United States, a country with minimal price controls, there is more pharmaceutical innovation than the European Union, a region with higher price controls. This is in the form of increased R&D spending, market authorizations for orphan drugs and new orphan drugs.

Although an increase in new 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. There are also loopholes within orphan drug policies that allow firms to reap benefits of market exclusivity and funding for products that do not target rare diseases.

Our study finds that the US spends more on domestic pharmaceutical R&D than the EU every year from 2004 to 2021. We find evidence of this also being true, on average after adjusting for GDP growth per capita. The US and EU both show a statistically significant increase in domestic pharmaceutical R&D spending annually, on average, between 2004 and 2021, after controlling for GDP growth per capita. We find evidence that the US increases this spending at a faster rate annually than the EU, on average. The mechanism that leads to this reduction in R&D spending is likely reduced profits due to price controls.

We hypothesized that reduced overall profits in the EU may incentivize an increased focus on orphan drug production because of market exclusivity and grant incentives to produce orphan drugs. However, we find that the US awards more market authorizations for orphan drugs than the EU every year between 2004 and 2021 except in 2007. Our study finds evidence that both the US and EU increase the number of annual market authorizations for orphan drugs on average between 2004 and 2021, after adjusting for GDP growth per capita, and that the US increases annual market authorizations at a faster rate. We also found evidence that an increase in R&D spending is associated with an increase in orphan market authorizations in both the EU and US, on average, however, our linear model shows evidence that the US awards more market authorizations per billion-dollar increase, on average. We should be cautious with this conclusion as our Poisson model finds no evidence of this association between annual domestic R&D spending and additional US orphan drug market authorizations compared to the EU. However, our linear model is a better fit to our observed data, so our linear model results that there is evidence of this association, seem more reliable.

It is likely cheaper to market authorize pre-existing drugs for new conditions rather than develop new drugs. Because the US market authorizes more pre-existing drugs for new diseases than the EU, we hypothesized that this may be why the US awards more orphan drug market authorizations per billion US dollars of R&D spending. After modeling market authorizations for new orphan drugs, we find that US firms market authorize more new orphan drugs than the EU every year between 2004 and 2021 except for in 2007. Results from our Poisson model of new orphan drug market authorizations show no evidence that the US increases annual market authorizations for new orphan drugs at a faster rate, on average between 2004 and 2021 than the EU, after adjusting for GDP growth rate per capita. We should be cautious with this conclusion as our linear model shows that there is evidence that the US increases market authorizations for new orphan drugs at a faster rate than the EU. However, our Poisson model is a better fit to our data, so we prefer our Poisson model results that there is not a significant difference in annual growth rates of market authorizations for new orphan drugs in the US and EU, on average.

Our linear model of new orphan drug market authorizations shows evidence that the US increases the number of market authorizations of new orphan drugs more per billion dollar increase in R&D spending, on average, after adjusting for GDP growth per capita between 2004 and 2021. We should be cautious with this conclusion as our Poisson model of new orphan drugs finds the opposite, that increased R&D spending is associated with reduced market authorizations for new orphan drugs, on average, after adjusting for GDP growth per capita in the US compared to the EU. However, our linear model is a better fit for our data, so our initial linear model results that the US increases the number of market authorizations of new orphan drugs more per billion dollar increase in R&D spending, on average, after adjusting for GDP growth per capita, seem more reliable.

This may indicate that the US allocates more R&D spending to the production of orphan drugs, compared to the EU. It also may be cheaper to produce new orphan drugs in the US compared to the EU, and the US may produce these drugs more efficiently. We would need to model overall drug production in order to deduce the cause of this difference. This would allow us to investigate if the relationship between R&D spending and orphan drug production is the same as overall drug production. However, both mechanisms point to policies being more effective in the US at stimulating the production of market authorizations for new orphan drugs.

While we can use our models to interpret how predictors are associated with the average number of annual orphan drug market authorizations between 2004 to 2021, we should be cautious of 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.

CHAPTER 6

FUTURE RESEARCH

**6.1 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 as new molecular entities (NME), new chemical entities (NCE), new therapeutic entities (NTEs), and new active substances (NAS). In order 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.

**6.2 Firm-Level Analysis**

Shaikh, Del Giudice, & Kourouklis (2020) found a negative association between EU market share and R&D intensity due to the negative association between price regulation and cash flow and profitability (Shaikh et al. 2020). 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 of the US and EU 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.

**6.3 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).

**6.4 R&D Intensity**

We can repeat the methods of our pharmaceutical R&D spending analysis on R&D intensity. R&D intensity measures the amount that a company or area spends on developing new drugs rather than other spending like the marketing of old drugs and stock buybacks. Golec & Vernon (2006) represented R&D intensity as R&D spending over total firm assets and explained that using assets rather than sales does not change results. They found that “U.S. firms have greater R&D intensity in all years [between 1993 to 2004] except 1995, 2003 and 2004” (Golec & Vernon, 2006, p. 11). Shaikh et al. (2020) and Vernon (2004) represented R&D intensity as the ratio of R&D expenditure to total sales within a firm.

R&D intensity is a valuable metric as it measures the amount that a company focuses on specifically developing new drugs. The U.S. House of Representatives Committee on Oversight and Reform 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” (Committee on Oversight and Reform U.S. House of Representatives, 2021, p. 164). Stock buybacks are an example of how spending may differ among firms that emphasizes why there is interest in studying R&D spending in relation to overall spending. However, we do not posit that stock buybacks themselves or other spending is good or bad 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, p. 3).

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APPENDIX

1. **Data and Code Repository**

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

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

1. **Unadjusted Models**

**Table B.1 Linear Models of Annual Domestic R&D Spending (Not Adjusted for Error Structure)**A table with numbers and text

Description automatically generated with medium confidence

*The standard errors listed in this table are not accurate as they have not been adjusted for the covariance of observations in time.*

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

**A paper with numbers and text

Description automatically generated with medium confidence**

*The standard errors listed in this table are not accurate as they have not been adjusted for the covariance of observations in time.*

**Table B.3 Poisson Models of Orphan Drug Market Authorizations (Not Adjusted for Error Structure)A table of statistics

Description automatically generated with medium confidence**

*The standard errors listed in this table are not accurate as they have not been adjusted for the covariance of observations in time.*

**Table B.4 Linear Models of Market Authorizations for New Orphan Drugs (Not Adjusted for Error Structure)**

A table with numbers and a number of text

Description automatically generated with medium confidence

*The standard errors listed in this table are not accurate as they have not been adjusted for the covariance of observations in time.*

**Table B.5 Poisson Models of Market Authorizations for New Orphan Drugs (Not Adjusted for Error Structure)**

A table of numbers and text

Description automatically generated with medium confidence

*The standard errors listed in this table are not accurate as they have not been adjusted for the covariance of observations in time.*

1. **Selected Residual Panels**

A group of graphs with lines

Description automatically generated with medium confidence

**Figure C.1 Linear Model 6 of Annual Domestic R&D Spending - Residual Plots**

A group of graphs with text

Description automatically generated with medium confidence

**Figure C.2 Linear Model 4 of Annual Domestic R&D Spending - Residual Plots**

A group of graphs with numbers

Description automatically generated with medium confidence

**Figure C.3 Linear Model 3 of Annual Orphan Drug Market Authorizations - Residual Plots**

A group of graphs showing the results of a linear model

Description automatically generated with medium confidence

**Figure C.4 Linear Model 4 of Annual Orphan Drug Market Authorizations - Residual Plots**

A group of graphs showing different types of drug

Description automatically generated with medium confidence

**Figure C.5 Poisson Model 3 of Annual Orphan Drug Market Authorizations**

A group of graphs showing the results of a model

Description automatically generated with medium confidence

**Figure C.6 Poisson Model 4 of Annual Orphan Drug Market Authorizations - Residual Plots**

A group of graphs showing different types of drugs

Description automatically generated

**Figure C.7 Linear Model 3 of Annual Market Authorizations for New Orphan Drugs - Residual Plots**

A group of graphs with text

Description automatically generated with medium confidence

**Figure C.8 Linear Model 4 of Annual Market Authorizations for New Orphan Drugs - Residual Plots**

A group of graphs with numbers

Description automatically generated with medium confidence

**Figure C.9 Poisson Model 3 of Annual Market Authorizations for New Orphan Drugs - Residual Plots**

A group of graphs showing different types of drugs

Description automatically generated

**Figure C.10 Poisson Model 4 of Annual Market Authorizations for New Orphan Drugs - Residual Plots**

1. **Variance Inflation Factors and Correlation Matirces**

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

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Area | Annual GDP per capita growth rate | Years after 2004 |
| VIF | 1.000047 | 1.023572 | 1.023525 |

**Table D.2 VIFs of Predictors for Models of Orphan Drug Market authorizations**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Area | Annual GDP per capita growth rate | Years after 2004 | Annual Domestic R&D Spending |
| VIF | 4.960278 | 1.064648 | 4.472835 | 8.341983 |

**Table D.3 Correlation Matrix of Predictors for Models of Orphan Drug Market Authorizations**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Years after 2004 | Annual Domestic R&D Spending | Annual GDP per capita growth rate |
| Years after 2004 | 1.0 | 0.632 | -0.152 |
| Annual Domestic R&D Spending | 0.632 | 1.0 | -0.023 |
| Annual GDP per capita growth rate | -0.152 | -0.023 | 1.0 |

1. **Selected Code**

Code of the full models from each analysis section are listed below.

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

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

```{r}

mod.rd.6 <- lm(annual\_domestic\_RD\_spending\_bil\_dollars ~ as.factor(area) + gdp\_per\_capita\_annual\_growthrate\_usd + yearsafter2004 + yearsafter2004:as.factor(area) + +I(yearsafter2004^2) + I(yearsafter2004^2):as.factor(area), 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")

```

plot\_linear\_rd() and get\_rd\_model\_metrics() are functions available in the git repository listed in appendix A

**E.2 Linear Model 5 of Number of Annual Orphan Drug Market Authorizations**

## Linear Model 5 of Num of Annual Orphan Drug MAs

```{r}

mod.od.5 <- lm(freq\_orphan\_drug\_mas ~ as.factor(area) + yearsafter2004 + annual\_domestic\_RD\_spending\_bil\_dollars + gdp\_per\_capita\_annual\_growthrate\_usd + as.factor(area):yearsafter2004 + as.factor(area):annual\_domestic\_RD\_spending\_bil\_dollars , data=combined\_rd\_ma\_df)

summary(mod.od.5)

plot\_lin\_pois\_od(mod.od.5, "5", "Linear")

#Estimate covariance matrix with Newey West

mod.od.5.vcov <- vcovPL(mod.od.5, cluster = ~ as.factor(combined\_rd\_ma\_df$area), lag="NW1994")

#Adjust standard errors based on estimated covariance matrix

mod.od.nw.5 <- coeftest(mod.od.5, vcov = mod.od.5.vcov)

mod.od.nw.5

#Get RMSE

predicted <- predict(mod.od.5, type = "response")

actual <- combined\_rd\_ma\_df$freq\_orphan\_drug\_mas

mod.od.5.rmse <- rmse(actual=actual, predicted=predicted)

confint(mod.od.nw.5)

mod.od.5.metrics <- get\_od\_model\_metrics(mod.od.5, "Linear")

```

plot\_lin\_pois\_od() and get\_od\_model\_metrics() are functions available in the git repository listed in appendix A

**E.3 Poisson Model 5 of Number of Annual Orphan Drug Market Authorizations**

## Poisson Model 5 of Num of Annual Orphan Drug MAs

```{r}

mod.pois.od.5 <- glm(freq\_orphan\_drug\_mas ~ as.factor(area) + yearsafter2004 + annual\_domestic\_RD\_spending\_bil\_dollars + gdp\_per\_capita\_annual\_growthrate\_usd + as.factor(area):yearsafter2004 + as.factor(area):annual\_domestic\_RD\_spending\_bil\_dollars, 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)

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 available in the git repository listed in appendix A

**E.4 Linear Model 5 of Annual Number of Market Authorizations for New orphan drugs**

## Linear Model 5 of Annual MAs for NEW orphan drugs

```{r}

mod.new.od.5 <- lm(freq\_new\_orphan\_drug\_mas ~ as.factor(area) + yearsafter2004 + annual\_domestic\_RD\_spending\_bil\_dollars + gdp\_per\_capita\_annual\_growthrate\_usd + as.factor(area):yearsafter2004 + as.factor(area):annual\_domestic\_RD\_spending\_bil\_dollars, data=combined\_rd\_ma\_df)

summary(mod.new.od.5)

plot\_lin\_pois\_new\_od(mod.new.od.5, "5", "Linear")

#Estimate covariance matrix with Newey West

mod.new.od.5.vcov <- vcovPL(mod.new.od.5, cluster = ~ as.factor(combined\_rd\_ma\_df$area), lag="NW1994")

#Adjust standard errors based on estimated covariance matrix

mod.new.od.nw.5 <-coeftest(mod.new.od.5, vcov = mod.new.od.5.vcov)

mod.new.od.nw.5

mod.new.od.5.metrics <- get\_new\_od\_model\_metrics(mod.new.od.5, "Linear")

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

```

plot\_lin\_pois\_new\_od() and get\_new\_od\_model\_metrics() are functions available in the git repository listed in appendix A

**E.5 Poisson model 5 of Annual Number of Market Authorizations for New orphan drugs**

## Poisson model 5 of Annual Num of MAs for NEW orphan drugs

```{r}

mod.pois.new.od.5 <- glm(freq\_new\_orphan\_drug\_mas ~ as.factor(area) + yearsafter2004 + annual\_domestic\_RD\_spending\_bil\_dollars + gdp\_per\_capita\_annual\_growthrate\_usd

+ as.factor(area):yearsafter2004 + as.factor(area):annual\_domestic\_RD\_spending\_bil\_dollars, data=combined\_rd\_ma\_df, family=poisson(link="log"))

summary(mod.pois.new.od.5)

plot\_lin\_pois\_new\_od(mod.pois.new.od.5, "5", "Poisson")

#Estimate covariance matrix with Newey West

mod.pois.new.od.5.vcov <- vcovPL(mod.pois.new.od.5, cluster = ~ as.factor(combined\_rd\_ma\_df$area), lag="NW1994")

#Adjust standard errors based on estimated covariance matrix

mod.pois.new.od.nw.5 <- coeftest(mod.pois.new.od.5, vcov = mod.pois.new.od.5.vcov)

mod.pois.new.od.nw.5

mod.pois.new.od.5.metrics <- get\_new\_od\_model\_metrics(mod.pois.new.od.5, "Poisson")

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

```

plot\_lin\_pois\_new\_od() and get\_new\_od\_model\_metrics() are functions available in the git repository listed in appendix A