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

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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.  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 first aim of this study is to examine the differences in domestic R&D spending in the EU and US in recent years. We find that the US spends more on domestic pharmaceutical R&D than the EU every year between 2004 and 2021. The US also increases annual domestic pharmaceutical R&D spending at a faster rate than the EU, on average, after adjusting for GDP growth per capita during this time frame. In prior studies, this reduction in domestic R&D has been shown to lead to less new drug production. Prior studies have focused on the production of all pharmaceutical products, but our study aims to identify the relationship between US and EU policies, price controls, and spending on orphan drug production. Orphan drugs are pharmaceutical products that treat rare diseases and the US and EU. Both the EU and US aim to stimulate orphan drug production with policies including national grants 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 need to rely on these orphan drug perks while in the EU, firms may take further advantage of orphan drug incentives. However, we find that the US awards more market authorizations for new orphan drugs than the EU, on average between 2004 and 2021, after adjusting for GDP growth per capita but not evidence that the US increases the rate of doing so faster than the EU. The US also awards more market authorizations for pre-existing orphan drugs to treat other diseases than the EU, on average, after adjusting for GDP growth per capita. This means that previously developed orphan drugs are being authorized for other diseases more in the US than the EU. We also find that an increase in domestic annual R&D spending is associated with the US producing more market authorizations for new orphan drugs and market authorizations for all orphan drugs than 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 compared to other drugs than firms in 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. Our results point to EU price controls and policies reducing new pharmaceutical innovation in the form of R&D spending, new orphan drugs, and market authorizations of pre-existing orphan drugs for new diseases, compared to in 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

In 2007, Abbot 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 [(Research and Development)]” (p. 29). 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 effect of price controls on the development and sale of orphan drugs, pharmaceutical products that target rare diseases (Orphanet, *About Orphan Drugs*, n.d.). The US and 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 the impact of differing policies in the United States and European Union on the number of orphan drugs authorized for sale. Vernon’s study concluded in 2007, so we hope to 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

**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 (US), pharmaceutical prices are “largely unregulated” (Vernon, 2004, p. 3), while in other countries, specifically in the European Union (EU), 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 affects 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.

Golec & Vernon (2006) investigated firm-level R&D spending and intensity, firm-level stock prices, and region-level R&D spending and intensity in the United States and European Union. Through studies of firm-level R&D, they found that in 1986, “EU pharmaceutical R&D [spending] exceeded US R&D by about 24 percent, but by 2004, EU R&D [spending] trailed US R&D [spending] by about 15 percent” (Golec & Vernon, 2006, p. 2). Between 1993 to 2004, US R&D spending was greater than EU R&D spending every year.

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 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.

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 “[m]ajor European firms have moved their research or operational headquarters to the U.S… [due to] growing U.S. sales compared to EU sales, and requirements that they perform clinical trials in the United States, particularly FDA phase three trials. U.S.-based trials also establish relationships with top U.S. physicians who set prescription guidelines for other physicians” (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. 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) thus, overall US and EU domestic spending is well represented by this data. However, differences in these organizations’ representations of the EU and US pharmaceutical markets may impact our conclusions when comparing their member’s R&D spending. We used this data to perform our analysis of domestic R&D spending in the EU and US.

Alongside EFPIA and PhRMA domestic R&D spending analysis, Golec & Vernon (2006) used findings from Doukas and Switzer (1992), who showed that “announcements of increases in planned R&D expenditures are associated with significant positive…stock returns” (Doukas and Switzer, 1992, p. 1). Golec and Vernon explained that if price controls impact R&D, there will be differences in EU and U.S. pharmaceutical stock prices. They used total and risk-adjusted returns and found that U.S. pharmaceutical stocks outperformed EU stocks after 1997 until 2004. In 2004, the U.S. price index continued to lead the EU price index, but “the EU price index increase[d] substantially more than the U.S. index” (Golec & Vernon, 2006, p. 15). This contrast between annual spending and annual growth rates of spending highlight the importance of growth rates as a metric alongside annual R&D spending. This analysis ended in 2004, so our study replicates some of their procedures with recent data.

R&D spending leads to the creation of new drugs. “Studies have estimated that the R&D cost for a new drug ranges from $314 million to $4.46 billion, depending on the therapeutic area, 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 nationally (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 “lack of knowledge about these diseases, the longer clinical development time due to difficulty in enrolling patients, and the need to depart from traditional clinical 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. 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, which may be reduced to 6 years if the product is sufficiently profitable), protocol assistance and follow-up, available study funding and national grants, and reduced or waived regulatory fees. 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), protocol assistance and follow-up, reduced or waived regulatory fees, tax credit 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, “out-of-pocket clinical costs per approved orphan drug [were found] to be $166 million and $291 million (2013 USD) per non-orphan drug. The capitalized clinical costs per approved orphan drug and non-orphan drug were estimated to be $291 million and $412 million, respectively. When focusing on new molecular entities only…the capitalized clinical cost per approved orphan drug was half that of a 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 cost of clinical trials.” (Austin and Hayford, 2021, p. 37)

In the European Union, benefits vary between countries. For example, “orphan medicines qualify for exemption from the national tax on pharmaceuticals and clawbacks in Belgium, and pricing and reimbursement is faster. Bulgaria provides some public funding for orphan drugs, and in Croatia, very expensive medicines, including orphans, are financed from 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 found that pharmaceutical product returns decline sharply after patent expiration due to competition with generics (Grabowski & Vernon, 1990). This suggests that a longer period of market exclusivity will likely increase returns on pharmaceutical products. The market exclusivity awarded to orphan drugs may result in a different R&D trend compared to that of all pharmaceutical products. Because of differing periods of market exclusivity for orphan drugs in the US and EU, this may impact the desire to produce these drugs differently in each region.

**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 extensive 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**  “The act offers tax credits, a waiver of the Prescription Drug User Fee, and extended market exclusivity for orphan drugs in the US” (Roberts and Wadhwa, 2021, p. 1) |
| 1985-1990 |  | **1985 and 1990 amendments of the Orphan Drug Act**  “The definition of orphan product was extended to products other than drugs and in particular: biologics, medical devices and medical foods, mainly parenteral nutrition and nutraceuticals.” (Orphanet, *Orphan Drugs in the United States of America*, n.d., para 7) |
|  |  | **1992 amendment of the Orphan Drug Act**  “If the drug is theoretically similar to an orphan drug authorised for the same rare disease, the applicant must demonstrate the clinical superiority of this drug… [Additionally, m]ore than one sponsor can receive designation for the same drug for the same use; the seven year marketing exclusivity is given to the first sponsor to file a complete NDA. Competitors are not prevented from making the drug available for different uses during the seven year period of exclusivity.” (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 EU. (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 ten-year period of orphan market exclusivity should be extended to twelve years if the requirement for data on use in the paediatric population is fully met.” (Publications Office of the European Union, 2006, para. 29) |  |
| 2017 |  | **2017 Tax Act**  This act “reduced the tax credit created by the Orphan Drug Act from 50 percent to 25 percent of the cost of clinical trials” (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. 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, “On March 23, 2020, the US Food and Drug Administration (FDA) granted Gilead Science an orphan drug designation for remdesivir to treat coronavirus disease 2019...at the time of Gilead’s application for designation, there were sufficiently few confirmed cases of COVID-19 in the United States…A group of 51 advocacy organizations wrote a letter to the chief executive officer of Gilead, calling the designation an ‘unconscionable abuse’ of orphan drug policy. Perhaps due to the intense public backlash, Gilead asked the FDA to revoke the orphan drug designation” (Chua & Conti, 2020, para. 2). In this case, had Gilead not requested the revoking of this designation, there would have been little precedent for the FDA to do so had they determined that this low number of cases was due to under-testing or if cases grew above 200,000 cases eventually, as designations are based on the number of affected individuals at the time of an orphan designation application. Companies can reap benefits reserved for rare disease medicines when these diseases may affect many people, and this designation may lead to increased profits.

Additionally, firms can obtain many orphan designations for the same drug and can market this 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 “expand sales by obtaining new therapeutic indications, orphan or otherwise, while maintaining the initial price.” (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 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, but this also may be an avenue to reap excessive profits.

“EU law…allows a reduction of the exclusivity period to six years when a drug is deemed sufficiently profitable, though that authority has not been exercised” (Bagley et al., 2019, p. 132).  If this provision was utilized in the EU and US, some of these loopholes might be solved, but in the status quo, firms often exploit orphan drug policies to increase profits.

We hope to build upon existing research studying the relationship between price controls and research and development spending. We will investigate if this relationship is the same for drugs that target rare diseases. Because of policies incentivizing orphan drug production, we hypothesize that the production of orphan medicines in the United States and European Union will differ from overall R&D spending trends.

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. The population of the EU was 449.2 million in January 2024 (Eurostat, 2024) and the US’ population was 335.9 million (U.S. Department of Commerce, 2024). We can translate the population proportions necessary to achieve an orphan drug designation to be on the same scales through the following computations.

In the EU, orphan drug designations are awarded for drugs that treat less than 5 in 10,000 people in the EU. We can convert this to the total max population in the EU that an orphan drug can treat to compare to the US’ acceptance criteria.

As of January 2024, orphan drug designations are awarded for drugs that treat less than 224,600 people in the EU.

In the US, orphan drug designations are awarded for drugs that treat less than 200,000 people in the US. We can find the max population out of 10,000 people that an orphan drug can treat to compare to the EU’s acceptance criteria.

As of January 2024, the US accepts pharmaceuticals that treat less than about 6 in 10,000 people in the US while the EU accepts those that treat less than 5 in 10,000 people in the EU. The US accepts orphan drugs for diseases that affect a larger proportion of people in the area than the EU. This may imply that there is a slightly lower threshold to obtain an orphan drug designation in the US than the EU.

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. 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 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 (26 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 later in this chapter.

The following figure 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 year

Description automatically generated

**Figure 3.1 Annual Domestic R&D Spending by Year 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 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 1986-1997, and US spending exceeded EU spending from 1998-2004 (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 2004-2021.

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: year, area (US and EU), annual GDP growth rate per capita, interactions between these variables and polynomial transforms of the year variable. 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 year variable were included to capture the visual curvature in R&D spending.

The full model with all variables, is as follows.

Where:

is number of years after 2004.

specifies if the observation is from the US or EU.

.

is the annual GDP growth rate per capita, t years after 2004 for the specified area.

If a coefficient is positive and significant, there is evidence of a positive association between the variable and annual domestic R&D spending, on average between 2004 and 2021, after adjusting for the other predictors in the model. If the coefficient is negative and significant, there is evidence of a negative association.

We used the lm() function in R to estimate this model. Code for our full model in R is in the appendix…\_\_\_

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). We also considered models that best satisfy the assumptions of linear regression, as we discuss in section 3.4.

**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. Because of policies incentivizing the production of orphan drugs, it is not obvious if the number of orphan drugs produced will follow the same trend as domestic R&D. The total number of market authorizations for orphan drugs to be sold in the US and EU were counted by year. The market authorizations in Europe were obtained from Orphanet (Orphanet, *Lists of Medicinal Products for Rare Diseases in Europe,* 2021) and the market authorizations in the United States were obtained from the FDA (U.S. Food and Drug Administration (FDA), 2024).

First, we visualize the annual number of market authorizations of orphan drugs for sale in the EU and US. Market authorizations may be given to drugs that already have an orphan drug market authorization to treat a new disease. Later in this paper, we investigate market authorizations for new drugs. A graph showing the number of drug market

Description automatically generated

**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, when both the EU and US implemented 16 market authorizations for orphan drugs and 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: year, area (US/ EU), R&D spending, annual GDP growth rate per capita and interactions between these variables.

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

Where:

is number of years after 2004.

specifies if the observation is from the US or EU.

.

is the annual GDP growth rate per capita, t years after 2004 for the specified area.

is the annual domestic R&D spending, t years after 2004 for the specified area.

If a coefficient is positive and significant, there is evidence of a positive association between the variable and market authorizations for orphan drugs, on average between 2004 and 2021, after adjusting for the other predictors in the model. If the coefficient is negative and significant, there is evidence of a negative association.

We used the lm() function in R. The code for our full linear model of orphan drug market authorizations is in the appendix…\_\_\_

We tested models with different combinations of these variables to analyze if these predictors are robust to variable additions. We chose best linear models using the model’s Akaike Information Criterion (AIC) and analysis of if the assumptions of linear regression were met by our model.

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 they use a log link function (Jabeen, 2019). We use our linear models as the linear predictors of our Poisson generalized linear models and use a log link function.

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

with the same variable descriptions as our linear models.

If a coefficient is positive and significant, there is evidence of a positive association between the variable and market authorizations for orphan drugs, on average between 2004 and 2021, after adjusting for the other predictors in the model. If the coefficient is negative and significant, there is evidence of a negative association.

We use the glm() function in the stats package in R with family=poisson(link="log"). The code for our full Poisson generalized linear model of orphan drug market authorizations in is in the appendix…\_\_\_

We chose best Poisson models using the models’ Akaike Information Criterion (AIC) and analysis of if the assumptions of generalized linear regression were met by our model. Because AIC is calculated based on the log likelihood of the model, Poisson generalized linear models and linear models cannot be directly compared using AIC. Thus, we also compare the root mean squared error (RMSE) of each model to get a straightforward measurement of how far the observed data is from our model. RMSE is interpretable and has the same units as the response variable. RMSE does not penalize more complex models with a greater number of predictors so we should use it only to compare Poisson and linear models with the same predictors. We use a combination of RMSE, AIC, and model assumption validation to choose the best linear and Poisson models.

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

There are many orphan drugs in the US that have several market authorizations for different treated diseases. Below is a list of US orphan drugs with over five market authorizations. There are 223 orphan drugs in the US with over one market authorization.

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

A table of information with text

Description automatically generated with medium confidence

In contrast, in Europe, there are three orphan drugs with over one market authorization. Below is a list of US orphan drugs with over one market authorization.

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

A close-up of a list of drugs

Description automatically generated

Because of this discrepancy, we also want to investigate the factors influencing the number of new orphan drugs each year alongside the previous analysis of number of market authorizations each year. If the US or EU were to produce more market authorizations for orphan drugs but less market authorizations for new orphan drugs, we must consider the societal benefit of creating a new pharmaceutical substance compared to the benefit of studying the use of an existing drug for a different condition.

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

Description automatically generated

**Figure 3.3 Annual Frequencies 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.

A graph showing the number of drug market authorities

Description automatically generated

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

Because there are few orphan drugs with multiple market authorizations in the EU, there is not a large 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 Frequencies of Market Authorizations for New Orphan Drugs in the EU and US**

The US still has 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.

* 1. **Model Assumptions**

After performing these regressions, we must check the assumptions of linear regression. 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. After training our models, we isolate the residuals of observations in the US and EU and evaluate the following assumptions.

* + 1. **Linearity between the combination of predictors and the response variable, constant variance of residuals, and normally distributed residuals**

We must confirm that there is a linear relationship between the explanatory variables and R&D spending. Model residual plots show a constant mean when this linear relationship exists. The assumption of constant variance of errors can be validated by a residual plot with an even distribution of residuals about their mean. These residuals should also be normally distributed at each combination of predictor values. This can be validated with a QQ-plot of residuals. We should have a strong correlation between the distribution of residuals at each fitted value and the theoretical normal distribution. The QQ plot would show a roughly straight, diagonal line if this normality exists (Ford, 2015).

**3.4.2 Multicollinearity of predictors**

When predictors are correlated, the variance of a regression coefficient can be inflated. To view the impact of this collinearity, we can calculate variance inflation factors (VIFs) of predictors. “VIFs represent the factor by which the correlations amongst the predictors inflate the variance.” (Frost 2020) VIFs < 5 imply low multicollinearity (Repala, 2023). Variance inflation factors (VIFs) 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.

**3.4.3 Independence of residuals**

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 true covariance matrix of observations with the assumption that the covariance between observations decreases as the time between observations increases. This corrected covariance matrix is then used to calculate the standard errors of our coefficient estimates which are used to calculate p-values. This method does not change the coefficients of a regression model, only the associated standard errors.

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. 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 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.

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. These standard errors of the model coefficients have been adjusted for the correlation of observations in time with the Newey-West estimator. Unadjusted models are in the appendix \_\_\_.

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

**A table with numbers and a number of text

Description automatically generated with medium confidence**

Variance inflation factors are computed for model 3, the model with all predictors and no interactions or polynomials. All main effects have variance inflation factors below 1.03, showing no evidence of collinearity. These VIFs are listed in appendix \_\_\_. Our best model on a basis of AIC is model 6 which is plotted below.

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**

A group of graphs with lines

Description automatically generated with medium confidence

**Figure 4.2 Linear Model 6 of Annual Domestic R&D Spending - Residual Plots**

The polynomial term for year, included as a main effect and in an interaction with area, 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. Model 4 does not contain this polynomial term.

**A graph with blue and orange dots

Description automatically generated**

**Figure 4.3 Linear Model 4 of Annual Domestic R&D Spending**

A group of graphs with text

Description automatically generated with medium confidence

**Figure 4.4 Linear Model 4 of Annual Domestic R&D Spending - Residual Plots**

Model 4’s residuals have a visually non-constant mean, violating the linearity assumption of linear regression. Thus, we should prefer model 6 when interpreting coefficients. While model 4 does not fit the curvature of our response, it does look to accurately fit the overall increasing trends of domestic R&D spending.

We adjust the standard errors of our models by calculating them with a Newey-West estimated covariance matrix of errors. Residual plots of models 1 through 5 show non-stationarity as they fail to account for the curvature in our trend, so Newey-West adjusted standard errors may not be accurate for these models. Model 6 residuals look to be stationary and visually pass the assumptions of linear regression.

The variable, US remains positive and significant in every model, before and after adjusting for years and GDP growth rate per capita. This indicates that there is strong evidence that the US spends more on annual domestic pharmaceutical R&D than the EU on average between 2004 and 2021 after adjusting for the areas’ overall economic growth. This gives us insight into the isolated association between price controls and pharmaceutical policies and domestic R&D spending.

The positive and significant estimate of the interaction between US and years after 2004 squared () in model 6 and the positive and significant estimate of the interaction between US and years after 2004 () in models 4 and 5, provides strong evidence that the US increases annual domestic pharmaceutical R&D spending at a faster rate annually on average between 2004 and 2021 compared to the EU before and after adjusting for annual GDP growth rate per capita. becomes negative in model 6 but this can be attributed to the addition of the higher order term, . The years after 2004 () variable is also positive and significant in every model, except model 6 when the also positive and significant higher order term, years after 2004 squared ( is added to the model. This tells us that there is strong evidence that the EU increases domestic R&D annually, on average between 2004 and 2021 although, the EU does so at a lower rate than the US. Visualizations of models 4, 5 and 6 show that they do accurately fit the overall trend of domestic R&D spending, especially model 6.

As Vernon (2004) and Vernon (2003) found, largely unregulated pharmaceutical prices in the US compared to the EU lead to higher cash flows, profits, and profit expectations. We suspect that this is why we see significantly more domestic R&D spending in the US than in the EU.

R&D spending directly leads to the creation of new drugs. Sertkaya et al (2024) finds 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 model 5 because of polynomial year terms. Model 4 does look to still capture the overall increasing trend of domestic R&D spending. 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 0.17 to 6.6 new drugs in annual new drug growth compared to the last year in the EU compared to the US from 2004 to 2021.

Without accounting for the different slopes of R&D spending in the US and EU, we can look at model 3 which only investigates the overall slope of average R&D spending in the US and EU from 2004 to 2021. The coefficient for the difference between the EU and US intercept () 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 dollars more annually than the EU on domestic pharmaceutical R&D on average, after adjusting for GDP growth per capita. 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.

While we can use our models to interpret how predictors are associated with average annual domestic R&D spending between 2004-2021, we should be cautious of predicting future R&D spending due to our small sample size and potential ceilings of R&D spending growth.

**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, annual GDP growth rate per capita, annual domestic R&D spending, and interactions between these predictors. The standard errors of the model coefficients have been adjusted for the correlation of observations in time with the Newey-West estimator. Unadjusted models are in the appendix \_\_\_.

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

**A table with numbers and a number of text

Description automatically generated with medium confidence**

Variance inflation factors are computed for model 2, the model with all predictors and no interactions. Annual GDP per capita growth rate had a VIF of about 1, area and years had VIFs of about 5, and annual domestic R&D spending had a VIF of about 8. These VIFs are listed in appendix \_\_\_. When calculating the correlation matrix as shown in appendix \_\_\_, annual domestic R&D spending has a correlation of about 0.63 with years. We confirmed that this linear association 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, and, the years: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.

A graph of a number of drugs

Description automatically generated with medium confidence

**Figure 4.5 Linear Model 3 of Annual Orphan Drug Market Authorizations**

A group of graphs showing different types of plots

Description automatically generated with medium confidence

**Figure 4.6 Linear Model 3 of Annual Orphan Drug Market Authorizations - Residual Plots**

A graph showing the number of drug manufacturers

Description automatically generated with medium confidence

**Figure 4.7 Linear Model 4 of Annual Orphan Drug Market Authorizations**

A group of graphs showing the results of a model

Description automatically generated with medium confidence

**Figure 4.8 Linear Model 4 of Annual Orphan Drug Market Authorizations - Residual Plots**

The positive and significant interaction between annual domestic R&D spending and the US in Model 4 indicates that there is strong 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. This may be because the US awards more market authorizations for the same drug than the EU, discussed in 4.3. It is likely cheaper to market authorize drugs that have been already developed for a new disease than develop a completely new drug. The coefficient of annual domestic R&D spending is also positive and significant, indicating strong evidence that an increase in annual domestic R&D spending is associated with more annual orphan drug market authorizations in the EU, although this increase is less than in the US.

The positive and significant interaction between year 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.

Model 1 shows a positive significant coefficient for the US variable (which becomes negative and significant when annual domestic R&D spending and years are added to the model in models 2 through 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 per capita was zero. However, the US has more market authorizations than the EU every year from 2004 to 2021. The linear property of our models means that when the slopes are better captured by adding years and R&D spending, the intercept is likely not able to be captured accurately.

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

We next use Poisson generalized linear models to attempt to better account for these potential linear modeling inaccuracies. Poisson models are often used for count data because they restrict the response variable to be above zero. They also can model some curvature that looks to exist in our data because a log link function is used. We compare linear and Poisson models with the same variables using root mean squared error (RMSE).

The following table displays five Poisson models of the annual number of orphan drug market authorizations with predictors; area (US/EU), years, annual GDP growth rate per capita, annual domestic R&D spending, and interactions between these predictors. The standard errors of the model coefficients have been adjusted for the correlation of observations in time with the Newey-West estimator. Unadjusted models are in the appendix \_\_\_.

**Table 4.3 Newey-West Adjusted Poisson Models of Orphan Drug Market AuthorizationsA table of numbers and text

Description automatically generated with medium confidence**

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

A graph of a graph showing the number of drugs

Description automatically generated

**Figure 4.9 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 4.10 Poisson Model 3 of Annual Orphan Drug Market Authorizations - Residual Plots**

**A graph showing the number of drug manufacturers

Description automatically generated**

**Figure 4.11 Poisson Model 3 of Annual Orphan Drug Market Authorizations**

**A group of graphs showing different types of drug

Description automatically generated with medium confidence**

**Figure 4.12 Poisson Model 4 of Annual Orphan Drug Market Authorizations - Residual Plots**

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. 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. However, both models 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.

The insignificant interaction between annual R&D spending and the US () in model 4 shows that there is not 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. This is a different conclusion than our linear model which showed evidence of a positive relationship between US spending and orphan drug market authorizations. 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, and we will conclude that there is evidence of an associated increase.

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 frequencies of orphan drug market authorizations due to our small sample size and potential ceilings of drug production.

**4.3 Market Authorizations for New Orphan Drugs**

Because we see a visual difference in the number of 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 new orphan drug market authorizations.

**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 with predictors; area (US/EU), years, annual GDP growth rate per capita, annual domestic R&D spending, and interactions between these predictors. The standard errors of the model coefficients have been adjusted for the correlation of observations in time with the Newey-West estimator. Unadjusted models are in the appendix \_\_\_.

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

**A table with numbers and a number of text

Description automatically generated with medium confidence**

As discussed in 4.2.1, because of correlated variables, year and R&D spending, we will look at 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 4.13 Linear Model 3 of Annual Market Authorizations for New Orphan Drugs**

A group of graphs with text

Description automatically generated with medium confidence

**Figure 4.14 Linear Model 3 of Annual Market Authorizations for New Orphan Drugs - Residual Plots**

**A graph showing the number of drugs

Description automatically generated**

**Figure 4.15 Linear Model 4 of Annual Market Authorizations for New Orphan Drugs**

A group of graphs showing the results of a model

Description automatically generated with medium confidence

**Figure 4.16 Linear Model 4 of Annual Market Authorizations for New Orphan Drugs - Residual Plots**

The positive and significant interaction between annual domestic R&D spending and the US in Model 4 indicates that there is strong 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 means that not only does the US increase orphan drug market authorizations more per billion dollar increase in R&D spending than the EU as found in section 4.2, but the US also increases market authorizations for new orphan drugs more per billion dollar increase in R&D spending than the EU.

This indicates that it may be cheaper in the US to produce new orphan drugs. 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.

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.

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

We will again also model this data using Poisson models due to its count nature to see if these models are a better fit. The following table displays five Poisson models of the annual number of market authorizations for new orphan drugs with predictors; area (US/EU), years, annual GDP growth rate per capita, annual domestic R&D spending, and interactions between these predictors. The standard errors of the model coefficients have been adjusted for the correlation of observations in time with the Newey-West estimator. Unadjusted models are in the appendix \_\_\_.

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

A table of numbers and text

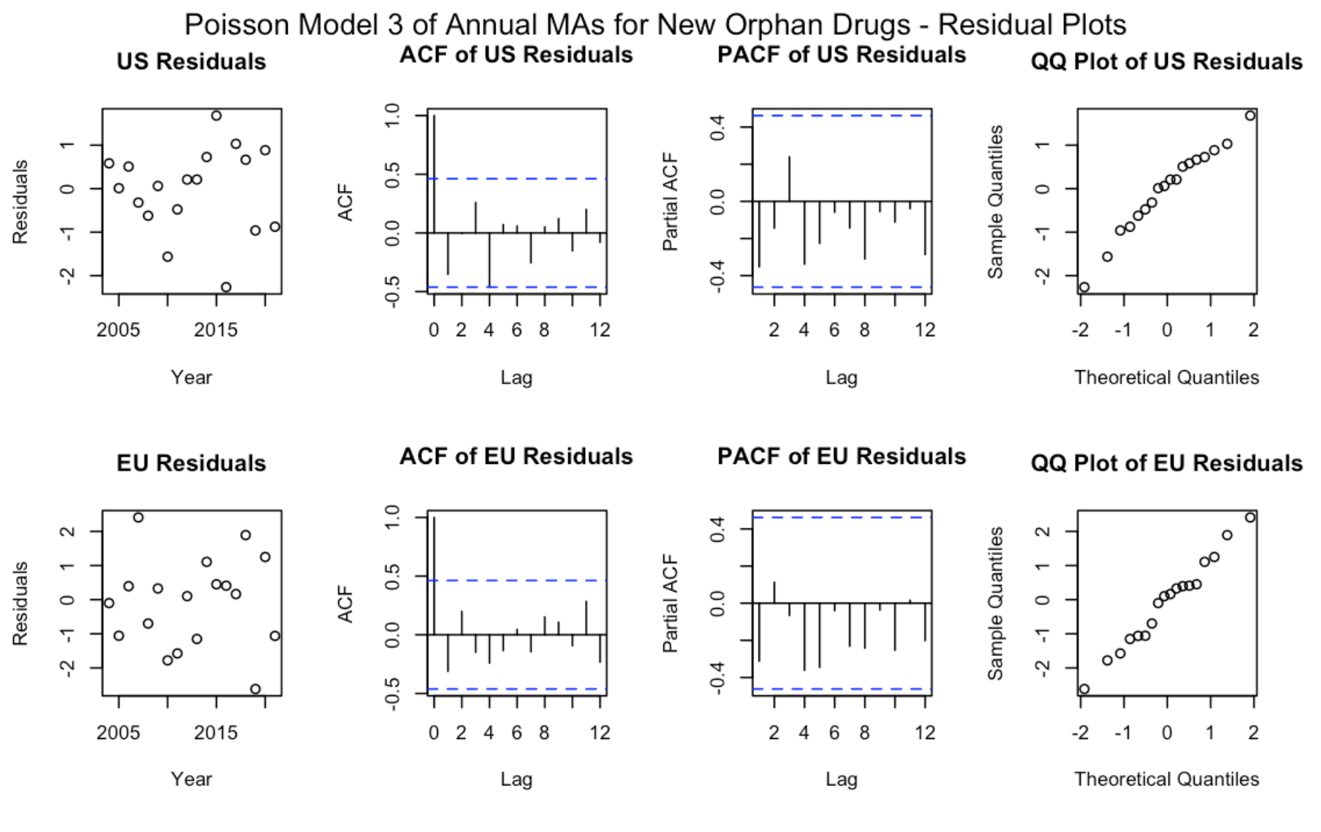
Description automatically generated with medium confidence

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

A graph of a graph showing the number of drugs

Description automatically generated with medium confidence

**Figure 4.17 Poisson Model 3 of Annual Market Authorizations for New Orphan Drugs**



**Figure 4.18 Poisson Model 3 of Annual Market Authorizations for New Orphan Drugs - Residual Plots**

A graph showing the number of drugs

Description automatically generated

**Figure 4.19 Poisson Model 4 of Annual Market Authorizations for New Orphan Drugs**

A group of graphs showing different types of drugs

Description automatically generated

**Figure 4.20 Poisson Model 4 of Annual Market Authorizations for New Orphan Drugs - Residual Plots**

The interaction between years and the US ( in model 3 is insignificant, showing no 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. This is a different conclusion from linear model 3, where 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 no 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.

The significant negative interaction between annual R&D spending and the US () in model 4 shows that there is evidence that an increase in R&D spending is associated with a lower number of market authorizations for orphan drugs in the US compared to the EU. This is a different conclusion than 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 the linear model 4 will be preferred over this Poisson model and we will conclude that there is evidence of an associated increase.

The intercept of US () 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. This slope is presumed to be insignificant in model 5 due to collinearity.

While we can use our models to interpret how predictors are associated with the average number of market authorizations for new orphan drugs between 2004 to 2021, we should be cautious of predicting future frequencies of market authorizations for new orphan drugs due to our small sample size and potential ceilings of drug production.

CHAPTER 5

CONCLUSION

Our study finds that the US spends more on domestic pharmaceutical R&D than the EU every year from 2004 to 2021. We find this to also be true, on average after adjusting for GDP growth per capita. We find evidence that the US and EU both increase 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 does so at a faster rate than the EU. This leads us to believe that the impact of pharmaceutical price controls is reduced domestic pharmaceutical R&D spending and spending growth. This directly leads to a loss of new drugs.

We hypothesized that reduced 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 when both awarded the same number of orphan drug market authorizations. Our study has found 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 does so 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 the EU and US however, our linear model shows evidence that the US awards more market authorizations per billion dollar increase. We should be cautious with this conclusion as our Poisson model finds no evidence of this association between annual domestic R&D spending and orphan drug market authorizations. However, our linear model is a better fit for our 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 so, because the US market authorizes more pre-existing drugs for new diseases than the EU, we thought this may be why the US awards more orphan drug market authorizations per billion dollars of R&D spending. After modeling market authorizations for new orphan drugs, we find that the US market authorizes more new orphan drugs than the EU every year between 2004 and 2021 except for 2007 when the EU authorized 15 new orphan drugs, and the US authorized 14. We find that there is 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 of new orphan drugs finds 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 for our data, so we prefer our Poisson model results that there is not a difference in annual new orphan drug market authorization growth rates in the US and EU.

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, after adjusting for GDP growth per capita. This may mean that the US allocates proportionally more R&D spending to the production of orphan drugs than other 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 see if the relationship between R&D spending and orphan drug production is the same as overall drug production. We should also 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 after adjusting for GDP growth per capita in the US compared to the EU, so we should be cautious about our conclusions. However, our linear model is a better fit for our data, so our initial linear model results seem more reliable.

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.

CHAPTER 6

FUTURE RESEARCH

**6.1 Causal inference**

In future research, we can study the annual difference in all new 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, drugs fall under different agencies, the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), under the FDA. 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) 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 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 correlated 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**

In future research on pharmaceutical R&D spending, we can repeat this 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 valuable 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, “[r]esults show that share repurchases are correlated with an increased likelihood that a given company will increase its research & development expenditure in the subsequent year following the repurchase” (Henning, 2018, p. 3).

REFERENCES/WORKS CITED/BIBLIOGRAPHY

Abbott, T. A., & Vernon, J. A. “The cost of US pharmaceutical price regulation: a financial simulation model of R&D decisions.” *Managerial and Decision Economics*, *28*(4-5), 293–306, 2007 <https://doi.org/10.1002/mde.1342>

Ao, Xiang. “Heteroskedasticity and Autocorrelation Consistent Standard Errors 1 Properties of OLS Estimator 1.1 When Is OLS Estimator Unbiased?” *Harvard Business School*, 2009.

Austin, David, and Tamara Hayford. “Research and Development in the Pharmaceutical Industry .” *Congressional Budget Office*, Apr. 2021, www.cbo.gov/publication/57126.

Bagley, N., Berger, B., Chandra, A., Garthwaite, C., & Stern, A. D. “The Orphan Drug Act at 35: Observations and an Outlook for the Twenty-First Century.” *Innovation Policy and the Economy*, *19*, 97–137, 2019 <https://doi.org/10.1086/699934>

Chen, A., & Obizhaeva, O. A. “Stock Buyback Motivations and Consequences: A Literature Review.” In *Google Books*. *CFA Institute Research Foundation*, 2022 <https://books.google.com/books?hl=en&lr=&id=bclgEAAAQBAJ&oi=fnd&pg=PT5&dq=stock+buybacks+bad&ots=3vg17JhEYg&sig=zL-mXrqycDLg6fYhZPbGdknaRsw#v=onepage&q=stock%20buybacks%20bad&f=false>

Chua, K.-P., & Conti, R. M. “Policy Implications of the Orphan Drug Designation for Remdesivir to Treat COVID-19.” *JAMA Internal Medicine*, 2020 <https://doi.org/10.1001/jamainternmed.2020.2759>

Committee on Oversight and Reform U.S. House of Representatives. “Drug Pricing Investigation Majority Staff Report.”, 2021 <https://oversightdemocrats.house.gov/sites/democrats.oversight.house.gov/files/DRUG%20PRICING%20REPORT%20WITH%20APPENDIX%20v3.pdf>

Côté, A., & Keating, B. “What Is Wrong with Orphan Drug Policies?” *Value in Health*, *15*(8), 1185–1191, 2012 <https://doi.org/10.1016/j.jval.2012.09.004>

Doukas, J., & Switzer, L. “The stock market’s valuation of R&D spending and market concentration.” *Journal of Economics and Business*, *44*(2), 95–114, 1992 <https://doi.org/10.1016/0148-6195(92)90009-y>

European Federation of Pharmaceutical Industries and Associations (EFPIA). “About Us.” Www.efpia.eu, [www.efpia.eu/about-us/](http://www.efpia.eu/about-us/).

---. The Pharmaceutical Industry in Figures. 2006.

---. “The Pharmaceutical Industry in Figures.” 2007, www.efpia.eu/media/15485/the-pharmaceutical-industry-in-figures-edition-2007.pdf.

---. “The Pharmaceutical Industry in Figures.” 2008, www.efpia.eu/media/15486/the-pharmaceutical-industry-in-figures-edition-2008.pdf.

---. “The Pharmaceutical Industry in Figures.” 2009, www.pharmine.eu/wp-content/uploads/2014/04/The\_Pharma\_Industry\_in\_figures\_Edition\_2009-20080612-009-EN-v1.pdf.

---. “The Pharmaceutical Industry in Figures.” 2010, [www.sfee.gr/wp-content/uploads/2015/05/Figures\_2010\_Final-20100611-001-EN-v1\_0.pdf. Accessed 30 Oct. 2024](http://www.sfee.gr/wp-content/uploads/2015/05/Figures_2010_Final-20100611-001-EN-v1_0.pdf.%20Accessed%2030%20Oct.%202024).

---. “The Pharmaceutical Industry in Figures.” 2011, www.efpia.eu/media/15489/the-pharmaceutical-industry-in-figures-edition-2011.pdf.

---. The Pharmaceutical Industry in Figures. 2012, www.sfee.gr/wp-content/uploads/2015/05/EFPIA\_Figures\_2012\_Final.pdf.

---. “The Pharmaceutical Industry in Figures.” 2015, www.efpia.eu/media/25822/2015-the-pharmaceutical-industry-in-figures.pdf.

---. “The Pharmaceutical Industry in Figures.” 2016, [www.efpia.eu/media/25055/the-pharmaceutical-industry-in-figures-june-2016.pdf](http://www.efpia.eu/media/25055/the-pharmaceutical-industry-in-figures-june-2016.pdf).

---. “The Pharmaceutical Industry in Figures.” 2017, [www.efpia.eu/media/219735/efpia-pharmafigures2017\_statisticbroch\_v04-final.pdf](http://www.efpia.eu/media/219735/efpia-pharmafigures2017_statisticbroch_v04-final.pdf).

---. “The Pharmaceutical Industry in Figures.” 2018 https://www.efpia.eu/media/361960/efpia-pharmafigures2018\_v07-hq.pdf, 2018.

---. “The Pharmaceutical Industry in Figures.” 2019, www.efpia.eu/media/412931/the-pharmaceutical-industry-in-figures-2019.pdf.

---. “The Pharmaceutical Industry in Figures.” 2020, www.efpia.eu/media/554521/efpia\_pharmafigures\_2020\_web.pdf.

---. “The Pharmaceutical Industry in Figures.” 2021, www.efpia.eu/media/602709/the-pharmaceutical-industry-in-figures-2021.pdf.

---. “The Pharmaceutical Industry in Figures.” 2022, www.efpia.eu/media/637143/the-pharmaceutical-industry-in-figures-2022.pdf.

---. “The Pharmaceutical Industry in Figures.” 2023, [www.efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf](http://www.efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf).

European Medicines Agency. “Committee for Orphan Medicinal Products (COMP) - European Medicines Agency.” *European Medicines Agency*, 17 Sept. 2018, [www.ema.europa.eu/en/committees/committee-orphan-medicinal-products-comp](http://www.ema.europa.eu/en/committees/committee-orphan-medicinal-products-comp).

FDA. “Rare Diseases at FDA.” FDA, 20 Feb. 2020, www.fda.gov/patients/rare-diseases-fda.

Ford, Clay. “Understanding QQ Plots | UVA Library.” Library.virginia.edu, 26 Aug. 2015, library.virginia.edu/data/articles/understanding-q-q-plots.

Frost, Jim. “Variance Inflation Factors (VIFs).” Statistics by Jim, 6 Dec. 2020, statisticsbyjim.com/regression/variance-inflation-factors/.

Golec, J., & Vernon, J. *NBER WORKING PAPER SERIES EUROPEAN PHARMACEUTICAL PRICE REGULATION, FIRM PROFITABILITY, AND R&D SPENDING*, 2006 <https://www.nber.org/system/files/working_papers/w12676/w12676.pdf>

Golec, J., & Vernon, J. A. “Financial Effects of Pharmaceutical Price Regulation on R&D Spending by EU versus US Firms.” *PharmacoEconomics*, *28*(8), 615–628, 2010 <https://doi.org/10.2165/11535580-000000000-00000>

Grabowski, H. G. “The Determinants of Industrial Research and Development: A Study of the Chemical, Drug, and Petroleum Industries.” *Journal of Political Economy*, *76*, 292–292, 1968 <https://ideas.repec.org/a/ucp/jpolec/v76y1968p292.html>

Grabowski, H., & Vernon, J. “A New Look at the Returns and Risks to Pharmaceutical R&D.” *Management Science*, *36*(7), 804–821, 1990 <https://www.jstor.org/stable/2632320?seq=18>

Gross, D. J., Ratner, J., Perez, J., & Glavin, S. L. “International pharmaceutical spending controls: France, Germany, Sweden, and the United Kingdom.” *Health Care Financing Review*, *15*(3), 127–140, 1994 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4193451/>

Hall, A. K., & Carlson, M. R. “The current status of orphan drug development in Europe and the US.” *Intractable & Rare Diseases Research*, *3*(1), 1–7, 2014 <https://doi.org/10.5582/irdr.3.1>

Henning, N. “Stock Buybacks and Innovation: An Analysis of the Effects of Stock Buybacks and Innovation: An Analysis of the Effects of Share Repurchases on Research & Development Expenditures Share Repurchases on Research & Development Expenditures.”, 2018 <https://creativematter.skidmore.edu/cgi/viewcontent.cgi?article=1138&context=econ_studt_schol>

Horgan, D., Koeva-Balabanova, J., Capoluongo, E., Jagielska, B., Cattaneo, I., Kozaric, M., Tumiene, B., El Ahl, J.-P., Lal, J. A., Kalra, D., & Malats, N. “Making Sure That Orphan Incentives Tip the Right Way in Europe.” *Healthcare*, *10*(9), 1600, 2022 <https://doi.org/10.3390/healthcare10091600>

Hyndman, Rob J., and George Athanasopoulos. “Forecasting: Principles and Practice, 2nd Edition.” *Otexts.com*, OTexts: Melbourne, Australia., 2018, otexts.com/fpp2/stationarity.html.

Jabeen, Hafsa. “Learn to Use Poisson Regression in R.” *Dataquest*, 27 Feb. 2019, www.dataquest.io/blog/tutorial-poisson-regression-in-r/.

Jayasundara, K., Hollis, A., Krahn, M., Mamdani, M., Hoch, J. S., & Grootendorst, P. “ Estimating the clinical cost of drug development for orphan versus non-orphan drugs.” *Orphanet Journal of Rare Diseases*, *14*(1), 2019 <https://doi.org/10.1186/s13023-018-0990-4>

Li, Lihua, et al. “Three Statistical Approaches for Assessment of Intervention Effects: A Primer for Practitioners.” *Risk Management and Healthcare Policy*, vol. Volume 14, Feb. 2021, pp. 757–70, <https://doi.org/10.2147/rmhp.s275831>.

Macrotrends. “Euro Dollar Exchange Rate (EUR USD) - Historical Chart.” 2024, www.macrotrends.net/2548/euro-dollar-exchange-rate-historical-chart.

---. “European Union GDP per Capita 1970-2024.” 2024, www.macrotrends.net/global-metrics/countries/EUU/european-union/gdp-per-capita.

---. “U.S. GDP per Capita 1960-2024.” 2024, [www.macrotrends.net/global-metrics/countries/USA/united-states/gdp-per-capita](http://www.macrotrends.net/global-metrics/countries/USA/united-states/gdp-per-capita).

Milne, C. -P ., and L. A. Cabanilla. “1.21 - Orphan Drugs and Generics.” ScienceDirect, edited by John B. Taylor and David J. Triggle, Elsevier, 1 Jan. 2007, pp. 655–80, www.sciencedirect.com/science/article/abs/pii/B008045044X000249.

Muldoon, Ariel. “Controlling Legend Appearance in Ggplot2 with Override.aes.” Very Statisticious, 9 July 2020, aosmith.rbind.io/2020/07/09/ggplot2-override-aes/.

Orphanet. “About orphan drugs.” <https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN>

---. “Lists of Medicinal Products for Rare Diseases in Europe.” 2021, www.orpha.net/pdfs/orphacom/cahiers/docs/GB/list\_of\_orphan\_drugs\_in\_europe.pdf.

---. “Orphan Drugs in the United States of America.” *Www.orpha.net*, [www.orpha.net/en/other-information/about-orphan-drugs?stapage=usa](http://www.orpha.net/en/other-information/about-orphan-drugs?stapage=usa).

Pharmaceutical Research and Manufacturers of America (PhRMA). 2022 PhRMA Annual Membership Survey. 2022.

---. “About.” Phrma.org, phrma.org/About.

Publications Office of the European Union. “EUR-Lex - 32006R1901 - EN - EUR-Lex.” Europa.eu, 2006, eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32006R1901.

---. “Regulation - 141/2000 - EN - EUR-Lex.” Eur-Lex.europa.eu, 2000, eur-lex.europa.eu/eli/reg/2000/141/oj.

Repala, Satya. “Tackling Multicollinearity: Understanding Variance Inflation Factor (VIF) and Mitigation Techniques.” *Medium*, 3 Aug. 2023, medium.com/@satyarepala/tackling-multicollinearity-understanding-variance-inflation-factor-vif-and-mitigation-techniques-2521ebf024b6.

Roberts, Alexis-Danielle, and Roopma Wadhwa. “Orphan Drug Approval Laws.” PubMed, *StatPearls Publishing*, 2021, [www.ncbi.nlm.nih.gov/books/NBK572052/](http://www.ncbi.nlm.nih.gov/books/NBK572052/).

Sertkaya, Aylin, et al. “Costs of Drug Development and Research and Development Intensity in the US, 2000-2018.” *JAMA Network Open*, vol. 7, no. 6, June 2024, p. e2415445, https://doi.org/10.1001/jamanetworkopen.2024.15445.

Shaikh, M., Del Giudice, P., & Kourouklis, D. “Revisiting the Relationship Between Price Regulation and Pharmaceutical R&D Investment.” *Applied Health Economics and Health Policy*, 2020 <https://doi.org/10.1007/s40258-020-00601-9>

Simoens, S. “Pricing and reimbursement of orphan drugs: the need for more transparency.” *Orphanet Journal of Rare Diseases*, *6*(1), 42, 2011 <https://doi.org/10.1186/1750-1172-6-42>

Sukumar, Gops. “AIC, BIC, Penalties and the Science behind Model Selection.” *Medium*, 15 Jan. 2024, medium.com/@gopal.sukumar/aic-bic-penalties-and-the-science-behind-model-selection-bd0d4d06d335.

The Biotechnology Industry Organization and the National Organization for Rare Disorders. “*Impact of the Orphan Drug Tax Credit on treatments for rare diseases”,* 2015 <https://rarediseases.org/assets/files/white-papers/2015-06-17.nord-bio-ey-odtc.pdf>

U.S. Department of Commerce. “Census Bureau Projects U.S. And World Populations on New Year’s Day.” U.S. Department of Commerce, 3 Jan. 2024, www.commerce.gov/news/blog/2024/01/census-bureau-projects-us-and-world-populations-new-years-day.

U.S. Food and Drug Administration (FDA). “Search Orphan Drug Designations and Approvals.” Fda.gov, 2024, www.accessdata.fda.gov/scripts/opdlisting/oopd/.

U.S. Government Publishing Office. “Amendment of 1986 Code.” Congress.gov, 2018, [www.congress.gov/115/plaws/publ97/PLAW-115publ97.htm](http://www.congress.gov/115/plaws/publ97/PLAW-115publ97.htm).

Van den Brand, Teun. “Ggplot2 3.5.0: Legends.” Tidyverse.org, 2024, www.tidyverse.org/blog/2024/02/ggplot2-3-5-0-legends/.

Vernon, J. The relationship between price regulation and pharmaceutical profit margins. *Applied Economics Letters*, *10*(8), 467–470, 2003 <https://econpapers.repec.org/article/tafapeclt/v_3a10_3ay_3a2003_3ai_3a8_3ap_3a467-470.htm>

Vernon, J. A. “Examining the link between price regulation and pharmaceutical R&D investment.” *Health Economics*, *14*(1), 1–16, 2004 <https://doi.org/10.1002/hec.897>

Żelewski, P., Wojna, M., Sygit, K., Cipora, E., Gąska, I., Niemiec, M., Kaczmarski, M., Banaś, T., Karakiewicz, B., Kotwas, A., Zabielska, P., Partyka, O., Pajewska, M., Krzych-Fałta, E., Bandurska, E., Ciećko, W., & Czerw, A. “Comparison of US and EU Prices for Orphan Drugs in the Perspective of the Considered US Orphan Drugs Act Modifications and Discussed Price-Regulation Mechanisms Adjustments in US and European Union.” *International Journal of Environmental Research and Public Health*, *19*(19), 12098, 2022 <https://doi.org/10.3390/ijerph191912098>

Zivot, Eric, and Jiahui Wang. *Modelling Financial Time Series with S-PLUS, Second Edition*. 2006, faculty.washington.edu/ezivot/econ589/manual.pdf.

APPENDIX

**Table 4.1 Linear Models of Annual Domestic R&D Spending (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.*

## 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")

```

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

## 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")

```

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

## 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")

```

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

A table of statistics 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.*

## 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)

```

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

A table of text with numbers

Description automatically generated with medium confidence

## 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)

```