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

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by

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ABSTRACT

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

in the US and EU

Bena Pearl Filipczak Smith

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

We observe that the largest US firms spend more on domestic pharmaceutical R&D than the largest EU firms 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 and year**. **We also find evidence that the US increases annual R&D spending at a faster rate than the EU between 2004 and 2021, on average, after adjusting for GDP growth per capita.** Prior studies have asserted that the impact of increased US spending is more pharmaceutical products. Our study aims to quantify the differences in US and EU 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. Our study gives indication that these policies are effective at spurring rare disease drug creation. **We find evidence that market authorizations for orphan drugs and market authorizations for new orphan drugs increase annually, on average, in both the US and EU from 2004 to 2021, after adjusting for GDP growth rate per capita.**

There may be different firm spending patterns for orphan drug development in the US and EU compared to overall R&D spending because of differing orphan drug policies and benefits. 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,the US awarded more annual orphan drug market authorizations and market authorizations for new orphan drugs than the EU every year from 2004 and 2021 except for in 2007. **We find evidence that from 2004 to 2021, the US awards more annual orphan drug market authorizations and market authorizations for new orphan drugs than the EU, on average, after adjusting for GDP growth per capita and year.** **There is also evidence that the US increases the number of these authorizations at a faster rate than the EU, annually, on average, after adjusting for GDP growth per capita.** Orphan drug policies do not seem to change US and EU pharmaceutical firm behavior much from overall R&D spending.

Our results point to an association between EU price controls 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 because of price controls.

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

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Chapter 1

INTRODUCTION

The United States is the only major pharmaceutical market where prices are largely unregulated. In every other major market, prices are regulated either directly or indirectly (Abbott & Vernon, 2005). The relationship between price controls and research and development (R&D) spending has been studied extensively; however, most of these studies concluded before 2007. We aim to first investigate if this relationship continues to exist in recent years by studying the differences in R&D spending in the United States (US) and European Union (EU).

Many studies have examined how increased R&D spending in the US translates to a greater number of new medicines sold to patients (Mulcahy, 2024). Few studies have evaluated if patients in the US also reap the benefit of more orphan drugs, pharmaceutical products that treat rare diseases (Orphanet, *About Orphan Drugs*, n.d.).

We quantify the differences in US and EU rare disease drug innovation by analyzing the counts of market authorizations for orphan drugs in both regions. Market authorizations (MAs) are given to orphan drugs that are approved for sale in the US and/or the EU by the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA), respectively. Lastly, because it is possible for an orphan drug to have multiple market authorizations, we model the EU and US’ counts of new orphan drugs that have not been previously market authorized for other rare diseases.

Chapter 2

LITERATURE REVIEW

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

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

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

Vernon (2004) explained that current cash flows and future profit expectations spur pharmaceutical R&D. In the United States, pharmaceutical prices are largely unregulated. In all other major pharmaceutical markets (Abbott & Vernon, 2005), specifically in the European Union, prices are regulated through price caps on products, profit controls, and limits on insurers’ reimbursement levels (Gross et al., 1994).

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

Lower prices make existing lifesaving and quality-of-life-improving medicines more accessible to patients, but they also reduce pharmaceutical company profits. Vernon (2003) found that pre-tax profits in the United States are, on average, approximately four times as large as those in non-US markets. A reduction in profits may lead to reduced spending on the R&D of new pharmaceutical products.

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 and 2004, US R&D spending exceeded EU R&D spending every year. (Golec & Vernon, 2006).

Shaikh, Del Giudice, & Kourouklis (2020) used the proportion of a pharmaceutical company’s 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) note that firms typically report only total R&D spending rather than domestic and international spending separately, complicating pharmaceutical spending analysis. They explain that many firms have moved their operations from the EU to the US due to greater sales in the US. There are also requirements that firms perform parts of the clinical trial process in the US and US-based trials help firms establish relationships with US physicians who set prescription standards (Golec & Vernon, 2006). To account for this, they used data from The Pharmaceutical Research and Manufacturers of America (PhRMA) and The European Federation of Pharmaceutical Industries and Associations (EFPIA), who report total and domestic R&D for their members by year. We used this data to perform our analysis of domestic R&D spending in the EU and US.

Most leading pharmaceutical companies are members of the PhRMA and EFPIA (Pharmaceutical Research and Manufacturers of America, n.d.) (European Federation of Pharmaceutical Industries and Associations, n.d.). However, 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 members’ 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 $327.0 to $773.2 million, including the costs of products that fail during the development process (Sertkaya et al 2024).

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

**2.2 Orphan Drugs**

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

Orphan drugs can be more difficult to develop than other pharmaceuticals because of limited knowledge of rare diseases, reduced numbers of patients to enroll in clinical trials, and the need to deviate from traditional study designs (ScienceDirect Topics, n.d.). 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 found a negative association between the prevalence of a disease and the cost of its treatment (Simoens, 2011).

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).

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

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

In the European Union, drugs with an orphan designation are allowed a 10-year market exclusivity period 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). Additionally, both the EU and US have pathways for accelerated approval of orphan drugs which meet a sufficient level of public health importance and innovation (Hall and Carlson, 2014).

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

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

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

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

|  |  |  |
| --- | --- | --- |
| **Year** | **EU Legislation** | **US Legislation** |
| 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.). |
| 1992 |  | **1992 amendment of the Orphan Drug Act**  For orphan drugs that are similar to currently authorized drugs, a firm must demonstrate the clinical superiority of the new product to receive an orphan designation. More than one sponsor can receive an orphan designation for the same drug. Market exclusivity is given to the first firm to file a new drug application. Designated orphan drugs may be sold by competitors during the period of market exclusivity for diseases outside of those the original firm has a designation for (Orphanet, *Orphan Drugs in the United States of America*, n.d.). |
| 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). |  |
|  | **Regulation (EC) No 726/2004 of the European Parliament and of the Council of March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency**  When a marketing authorization application is submitted for a medicinal product with major public health and innovation interest, the applicant may request an accelerated assessment procedure (European Parliament, Council of the European Union, 2004). |  |
| 2006 | **Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric 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). |  |
| 2012 |  | **Food and Drug Administration Safety and Innovation Act**  Expedites the development and review of new drugs that have preliminary clinical evidence that indicate substantial improvement over current treatments for patients with serious or life-threatening diseases. Such a drug is referred to as a “breakthrough therapy” (Hall and Carlson, 2014). |
| 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). |

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

Additionally, Grabowski and Vernon (1990) found that pharmaceutical product returns decline sharply after patent expiration due to competition with generics. This suggests that longer market exclusivity periods increase returns on orphan drugs. We hypothesized that longer periods of orphan drug market exclusivity in the EU may lead to more orphan drug production in the EU than the US, although this was not the finding of our statistical analysis.

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

Chapter 3

METHODS

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

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

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. In our models, 2004 is coded as year 0. Golec and Vernon’s similar 2006 study of domestic R&D spending from 1986 to 2004 had a one year longer study period than our analysis.

Figure 3.1 shows EFPIA and PhRMA member pharmaceutical domestic R&D spending. This spending is referred to as EU and US 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 with the average of 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 & Vernon (2006) observe that domestic EU R&D spending exceeded that of the US from 1986 to 1997, and US spending exceeded EU spending from 1998 to 2004. We can see visually that this trend has continued as the US outspent the EU in domestic pharmaceutical R&D every year from 2004 to 2021.

We view the slopes of US and EU R&D spending as visually parallel until 2014, when US R&D spending looks to increase at a faster rate than EU spending. This coincides with an increase in prescription spending in 2014. An overall pharmaceutical price increase occurred in the US and several EU countries however, it was most pronounced in the US (The Commonwealth Fund, 2017). We do not study this 2014 increase in price or R&D spending, but this observation aligns with our conjecture that increased prices may lead to increased R&D spending.

We analyze the average 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, region (US and EU), annual GDP growth rate per capita, polynomial transforms of the years after 2004 variable and interactions between year and region variables. Annual GDP growth rate per capita is used to capture and control for the overall economic performance of the US and EU (Macrotrends, *European Union GDP per Capita 1970-2024*, 2024) (Macrotrends, *U.S. GDP per Capita 1960-2024*, 2024). A polynomial transform of the years after 2004 variable is included to capture the visual nonlinearity in R&D spending.

The full model with all predictors is as follows:

Where:

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

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 region.

We test models with different combinations of these predictor variables to analyze if our coefficient estimates are robust to variable additions. We compared model performance using the Akaike Information Criterion (AIC) which measures the goodness of fit of our model while penalizing complex models with more parameters (Sukumar, 2024). This assessment of coefficient robustness, and AIC-based comparison process is used in all modeling performed in this study.

**3.2 Orphan Drug Market Authorizations**

Next, we analyze the difference in the annual number of market authorizations for orphan drugs in the US and EU. These are approvals by the US Food and Drug Administration or European Medicines Agency for orphan drugs to be sold to treat a specific disease or condition. Because of policies incentivizing the production of orphan drugs, it is not obvious if the number of market authorizations follows same trend as overall domestic R&D. The total number of market authorizations for orphan drugs to be sold in the EU and US are counted by year. Market authorizations in the EU are obtained from Orphanet (Orphanet, 2021) and market authorizations in the US are obtained from the FDA (U.S. Food and Drug Administration, 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 authorities

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

**EU and US**

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

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

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

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

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

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

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

**Table 3.1 US Market Authorization Counts for Orphan Drugs with Over 5 Orphan Drug 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 Counts for Orphan Drugs with Over 1 Orphan Drug Market Authorization**

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

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 of a drug market

Description automatically generated

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

Figure \_\_ shows a visual divergence between the trend of orphan drug market authorizations overall and market authorizations for new orphan drugs in the US.

A graph of a number of drug market authorities

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**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 the trend between orphan drug market authorizations overall and market authorizations for new orphan drugs in figure \_\_.

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

A graph showing the number of market authorities

Description automatically generated

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

The US still awarded more annual market authorizations for new orphan drugs than the EU in every year between 2004 to 2021, except in 2007. However, the slopes of authorizations over time 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 Poisson generalized linear models. Our response variable is now annual number of market authorizations for new orphan drugs.

**Collinearity of Predictors**

Variance inflation factors are calculated for all model main effects. We find that years, R&D spending, and region have VIFs greater than 2. Further visualizations of our predictors show potential collinearity between region and R&D spending because US R&D spending is consistently higher in the US compared to the EU. A visual of this correlation is in appendix \_\_. Because of this collinearity, we do not fit regressions containing both region and year as predictors.

There also looks to be correlation between years and R&D spending in figure \_\_ as R&D spending looks to increase over time. This is also confirmed via our models of R&D spending over time in \_\_\_. Thus, we also do not fit models with both R&D spending and years as predictors.

**3.5 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 standard errors for ordinary least squares estimates assume that residuals are independent. We estimate residual autocorrelation using the sample autocorrelation function (ACF) and sample partial autocorrelation function (PACF). If there is autocorrelation at any lag greater than lag zero, there is evidence that the assumption of residual independence has been violated. An example of a residual panel with evidence of autocorrelation is shown in appendix \_\_.

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

The Newey-West estimator is the most popular heteroskedasticity and autocorrelation consistent (HAC) estimator in economics and allows for a straightforward adjustment of standard errors (Ao, 2009). The Newey-West estimator is also easily applied to panel data and Poisson generalized model residuals (Zeileis and Lumley, n.d.). Because we are studying EU and US 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).

**Limitations**

**Non-Lagged R&D Spending**

Between 2010 and 2020, the median time to develop a pharmaceutical product was 8.3 years. (Brown et al., 2021) The R&D cost of a drug was likely spent several years before the product was brought to market. However, development time varies between drugs and R&D spending occurs throughout the development process. Our study focuses on the relationship between R&D spending and market authorizations in the same year rather than using lagged R&D spending as a predictor of orphan drug creation.

**Software Packages**

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

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

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

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 \_\_ have been adjusted using the Newey-West estimator. Unadjusted models are in appendix table\_\_\_.

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

**A table with numbers and numbers

Description automatically generated**

The models listed in Table \_\_ provide evidence that the US spent more on domestic pharmaceutical research and development, annually, on average, after and before adjusting for years after 2004 (henceforth referred to as years) and GDP growth per capita between 2004 to 2021. The US coefficient remains significant and positive in every model, robust to additions and removals 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 between 2004 to 2021. There is a positive and significant coefficient for years in every model except model 6. The years coefficient becomes insignificant in model 6 when the higher order term, years squared, is added to the model. This higher-order term is positive and significant in model 6, indicating the same conclusion, that there is evidence that the EU and US both increased R&D spending, on average, annually, after adjusting for GDP growth per capita between 2004 to 2021.

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

Our model with the lowest AIC is model 6, shown below in figure \_\_.

A graph with blue and orange dots

Description automatically generated

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

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

A graph of a number of years

Description automatically generated with medium confidence

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

The curvature of spending looks to be underrepresented in this model. However, conclusions of model 4 align with the more complex model 6. Although model 6 fit our model best, it is less interpretable than the other models because of polynomial year terms. Because the less complex models come to similar conclusions as the polynomial model, we use other models to interpret how differences in R&D spending may lead to different levels of drug production in the EU and US.

Sertkaya et al. (2024) estimates that the average R&D cost for developing a new drug is between $327.0 to $773.2 million, including the costs of failures.

Without accounting for the differing slopes of R&D spending in the EU and US, we can look at model 3 which only estimates the overall slope of average R&D spending in the US and EU from 2004 to 2021 and the average difference between annual EU and US R&D spending. The coefficient for the US indicator in model 3 has a 95% 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 19 and 85 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 95% 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 per capita. This is a potential loss of between 0.97 and 6.30 new drugs in average annual new drug growth, in the EU, compared to the US from 2004 to 2021.

**4.2 Orphan Drug Market Authorizations**

Next, we modeled the number of market authorizations for orphan drugs with linear models with different combinations of the predictors; region (US/EU), years after 2004, annual GDP growth 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 4.3 Newey-West Adjusted Poisson Models of Orphan Drug Market Authorizations**

**A table with numbers and a number of drug market authors

Description automatically generated with medium confidence**

The models listed in Table \_\_ provide evidence that the US market authorized more orphan drugs, annually, on average, after and before adjusting for years and GDP growth per capita between 2004 to 2021. The US coefficient remains significant and positive in every model, robust to additions and removals of other variables.

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

There is evidence that the US increased annual orphan drug market authorizations at a significantly faster pace than the EU, on average, after and before adjusting for annual GDP growth per capita between 2004 to 2021. The interaction between years and region is positive and significant in models 4 and 5.

**4.3 Market Authorizations for New Orphan Drugs**

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

The table \_\_\_ displays six 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 \_\_.

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

A table with numbers and a number of text

Description automatically generated with medium confidence

The models listed in Table \_\_ provide evidence that the US market authorized more new orphan drugs, annually, on average, after and before adjusting for years and GDP growth per capita between 2004 to 2021. The US coefficient remains significant and positive in every model, robust to additions and removals of other variables.

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

There is evidence that the US increased annual market authorizations for new orphan drugs at a significantly faster pace than the EU, on average, after and before adjusting for annual GDP growth per capita between 2004 to 2021. The interaction between years and region is positive and significant in models 4 and 5.

CHAPTER 5

ETHICAL CONSIDERATIONS

**High Prices**

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

For example, “Imiglucerase, an enzyme replacement therapy to treat Gaucher’s disease, 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 (2022) finds that orphan drug prices are typically higher in the US compared to the EU.

Our study should not serve as sufficient evidence that increased prices will benefit patients. High prices and company profits should be studied alongside our findings. Even if R&D spending does increase with higher prices, firms may still garner excessive profits and there may be courses of action to reduce prices without impairing the R&D of new drugs.

**Loopholes in Orphan Drug Policy**

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 sufficiently 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). Companies may unethically reap benefits reserved for rare disease medicines in order to collect excessive profits.

Firms can also obtain multiple orphan designations for the same drug and can market an orphan drug for non-rare diseases. “[O]f the 43 orphan drugs approved by the FDA whose global annual sales reached more than $1 billion, 18 had only one orphan designation, 15 had two, and 10 had three and more” (Côté & Keating, 2012, p. 1189). Côté and Keating found that firms may exploit orphan drug policies by obtaining an orphan designation and reaping economic benefits during the development, approval, and marketing phases. Then, firms obtain new therapeutic indications for other diseases including non-rare diseases. (Côté & Keating, 2012). For example, ibuprofen, which is widely used to manage various conditions, has received an orphan designation to treat the rare disease, patent ductus arteriosis (Hughes-Wilson et al., 2012).

In our analysis, we find that the EU rarely awards multiple orphan 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 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).  If this provision was utilized in the EU and US, some of these loopholes may be closed, but in the status quo, firms can exploit orphan drug policies to increase profits.

**Differences in Market Authorization Award Threshold**

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, 2024), the US acceptance criteria is equivalent to pharmaceuticals that treat less than about 6 in 10,000 people in the US. These similar thresholds might indicate that the EU and US have similar definitions of what an orphan drug may be used to treat.

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

CHAPTER 6

CONCLUSION

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

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

We observe that the US spent 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 and year. The EU and US both showed a statistically significant annual average increase in domestic pharmaceutical R&D spending, between 2004 and 2021, after controlling for GDP growth per capita. We find evidence that the US increased this spending at a faster rate annually than the EU, on average. The mechanism that led to this US improvement in R&D spending is likely increased profits due to limited price controls.

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

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

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

The US awarded more market authorizations for the same drug multiple times than the EU. In the US, there were 223 drugs with over one orphan drug market authorization whereas in the EU, there were nine. It may be a societal benefit to find multiple uses for the same drug, but this may divest focus from the research of new innovative products. Because of this authorization discrepancy between the US and EU, we analyzed the counts of orphan drugs that were receiving their first orphan drug market authorization. We find that the US still awarded more market authorizations for new orphan drugs than the EU every year between 2004 and 2021, except in 2007. We also find evidence that the US awarded more new orphan drug market authorizations than the EU, annually, on average, between 2004 and 2021, after adjusting for GDP growth per capita and year.

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

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

We posit that there appears to be an association between price controls and reduced innovation. However, the tradeoff is high prices. Côté & Keating (2012) find that even when orphan drugs receive a market authorization, they are often not reimbursed, limiting drug access unless patients pay high out of pocket prices. Because of the importance of R&D spending, Jayasundara (2019) proposes that drug prices could potentially be regulated based partially on R&D and production costs.

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

CHAPTER 7

FUTURE RESEARCH

**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).

**6.1 Firm-Level Analysis**

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

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

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

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

R&D intensity is a valuable metric as it measures 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 firms engage in spending outside of R&D. However, we do not posit that stock buybacks or other spending is detrimental or beneficial for society. Stock buybacks may be used as a tool to benefit top executives (Chen & Obizhaeva, 2022) however, share repurchases are correlated with increases in R&D spending in the year following the buyback (Henning, 2018).

**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 into categories including, new molecular entities (NME), new chemical entities (NCE), new therapeutic entities (NTEs), and new active substances (NAS). To perform effective causal inference on the impact of orphan drug policies, we should acquire data on all new pharmaceutical products in the US and EU.

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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 table with numbers and lines

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 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.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 text 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.*

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 | 1.00 | 1.02 | 1.02 |

**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 | 4.96 | 1.06 | 4.47 | 8.34 |

**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 | 1.00 | 0.63 | -0.15 |
| Annual Domestic R&D Spending | 0.63 | 1.00 | -0.02 |
| Annual GDP per capita growth rate | -0.15 | -0.023 | 1.00 |

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

