



Orphan Drug Utilization and Pricing Patterns (2012 - 2014)

DATA BRIEF

OCTOBER 2016

KEY TAKEAWAYS

44%
non-orphan
diseases

A sample of 45 orphan drugs available between 2012 and 2014 shows almost half of these drugs' usage—44 percent— was for non-orphan diseases.

24%
off-label

Across the three years of the study, on average 20 percent of orphan drug use was for non-orphan, on-label uses; while 24 percent was for off-label use.

42%
price
increases

Drugs having little-to-no orphan utilization increased their prices by 42% during the three-year study period; while, those orphan drugs used almost exclusively to treat orphan diseases increased prices by only 15%.

52%
price
increases

We also found that drugs having little-to-no off-label use increased their prices by only 16%; however, those drugs used extensively off-label increased their prices by 52% from 2012-2014.

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Summary

Orphan drugs- developed to treat rare diseases affecting patient populations of fewer than 200,000 people annually - have become a lucrative business opportunity for drug makers. These medications made up almost half of all new drugs approved by the U.S. Food and Drug Administration (FDA) in 2015

Given the growing number of orphan drugs currently in the market as well as the pipeline of future orphan treatments, understanding the utilization and pricing patterns of orphan drugs is of increasing interest to policymakers, public, and private payers given the potential cost impacts on the healthcare system. This study finds that price changes of certain orphan medications appear to be tied to the degree and type of utilization of the drug. Based on our sample of 45 orphan drugs available from 2012-2014, data show a significant, negative correlation between the magnitude of price changes and the degree of orphan utilization of these drugs. Furthermore, a significant positive correlation was detected between the magnitude of price changes and the degree of off-label use of these drugs. There was no significant correlation between price changes and the degree of FDA-approved, non-orphan uses of these agents. These findings suggest that the magnitude of off-label use may influence drug pricing.

These findings are supported by results from Analysis of Variance (ANOVA) testing which suggested that those orphan drugs having little to no orphan use, increased their prices significantly more than those orphan drugs used almost exclusively for treating orphan diseases. Similarly, those drugs having little-to-no off-label use, increased their prices less than those drugs having greater off-label use. Both ANOVA findings were statistically significant.

Background

Historically, pharmaceutical companies have focused their drug development efforts on widely prevalent health conditions given the level of investment required to develop and gain regulatory approval of a new prescription medication. But this practice often came at the expense of developing treatments for less commonly occurring illnesses.

Benefits of Orphan Drug Development

Passage of the Orphan Drug Act of 1983 (ODA), however, intensified the development of treatments for rare diseases, termed “orphan diseases.”^{1,2} The ODA, and its subsequent amendments, provided numerous incentives for drug makers willing to pursue the research and development of new therapies for these rare conditions, defined as those occurring in fewer than 200,000 people in the United States each year.¹⁻⁴ Among the benefits provided to orphan drug makers by the ODA are:

1. regular consultation between the FDA and the drug company regarding their orphan drug development progress and plans;
2. a waiver of the New Drug Application filing fee (\$2.4M for FY2016);
3. a 50 percent tax credit for all research and development expenditures incurred during the clinical testing of the orphan drug; and
4. a seven-year exclusivity period, beginning on the date of FDA’s approval of the orphan indication, during which time the FDA cannot approve another similar drug for the same orphan indication.¹⁻⁴

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In many respects, the ODA is widely regarded as a significant regulatory success as only a handful of orphan drugs had been approved in the years preceding it.^{5,6} However, as a result of the Act's direct incentives to drug companies, the development and approval of new orphan drugs has exploded during the three decades since the ODA took effect.^{5,6} More than 500 orphan drugs have been approved to-date, with hundreds more in development pipelines around the world.^{5,6} The FDA's recent report on its drug approvals for calendar year 2015 noted that of the 41 new drugs approved in 2015, almost half –19 new drugs – were approved for the treatment of orphan diseases.⁷ Moreover, the success of the ODA has motivated regulatory authorities in other countries, the European Union, Japan, Australia, and Canada, to develop similar orphan drug programs.⁸

In addition to the benefits listed above, drug companies typically spend less money developing orphan drugs. For example, given the rare nature of the orphan diseases, clinical trials for these drugs tend to be substantially smaller in size and thus, less costly.^{9,10} Moreover, the probability of FDA approval of orphan drugs has been significantly higher than non-orphan drugs; regulatory review times are significantly shorter; and once approved, marketing costs are substantially lower as only a small number of specialist physicians treat orphan disease patients.^{9,10} By offsetting the smaller market size with higher pricing, orphan drugs can generate incomes comparable to their non-orphan peers during the course of their product lifetimes.^{11,12} Thus, the pharmaceutical industry has embraced orphan drug development as an entirely new business model.⁹⁻¹²

Economic Impact of Orphan Drugs

Since the passage of the ODA, some have begun to raise questions about the unintended consequences of the orphan drug law, calling into question drug makers' pricing of orphan drugs.¹³⁻¹⁸ The combination of market exclusivity coupled with extremely high prices, many in excess of \$100,000 per year, has led to the creation of "blockbuster" orphan drugs, a result that seemingly runs counter to the original spirit of the legislation.¹⁹ Cote and Keating's 2012 study of more than 350 orphan drugs approved through mid-2010, found that 43 drugs, having at least one approved orphan indication, achieved global sales in excess of \$1 billion in 2008; and further, 33 other orphan drugs recorded global sales of \$100 million - \$999 million in 2008.¹⁹ The profitability of these medications is fueled by orphan drugs receiving approvals for other more prevalent non-orphan indications or capturing significant off-label use for other non-orphan diseases.

A recently published study by Divino and colleagues estimated that total US expenditures, in 2014 dollars, on all 356 brand-name orphan drugs approved in the US from 1983-2013, was \$15 billion in 2007 which increased to \$30 billion in 2013.²⁰ They note that such expenditures represented only 4.8 and 8.9

3 Step Strategy for Creating a Blockbuster Orphan Drug

Cote and Keating conclude, "It is clear from our analysis that actual legislations trigger a three-step strategy:

- 1. *apply for orphan designation, obtain substantial economic benefits during the development, approval and marketing phases, and demand a high price because of the low prevalence of the initial target population;***
- 2. *after approval, convince doctors to use the drug in their practice; and***
- 3. *expand sales by obtaining new therapeutic indications, orphan or otherwise, while maintaining the initial price.*"¹⁹**

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percent of total drug expenditures for 2007 and 2013, respectively.²⁰ It is important to note that Divino, *et al.* included only spending on each drug's orphan indications and did not include other, FDA-approved non-orphan indications or off-label uses in their calculations. Thus, their analyses appear to be understating the true financial impacts of these drugs.

Other researchers have investigated the clinical and economic impacts of off-label uses of drugs— uses not approved by the FDA. Radley, *et al.* examined nationally representative data from IMS Health finding that 150 million prescriptions out of 725 million total (21 percent) were for unapproved, off-label uses for 160 commonly used medications.²¹ Zarkali, *et al.*, investigated the frequency of off-label use of biologics and observed similar levels of off-label use of these therapeutics in the range of about 15-25 percent.²²

With respect to orphan drugs more specifically, Kesselheim, *et al.* examined the off-label use of four top-selling orphan medications: Lidoderm®; Provigil®; Sensipar®; and Gleevec®.²³ Based on medical and pharmacy claims data from 1999-2005, they found that orphan use of these medications made up a minority of use for all four drugs: 17.7 percent (Lidoderm®); 12.2 percent (Provigil®); 1.2 percent (Sensipar®); and 38.7 percent (Gleevec®).²³ Furthermore, they estimated that state Medicaid programs paid \$495 million for the unapproved, off-label use of just these four orphan drugs alone.²³

The off-label use of medications, be they orphan or non-orphan drugs, remains controversial. Radley, *et al.* found that of the 21 percent of drugs prescribed for off-label indications, only about 26 percent of those off-label uses had any scientific evidence to support such use.²¹ That is, about three-fourths of off-label use lacks any scientific evidence supporting such use. Although there are many examples of the beneficial uses of drugs off-label, there is growing concern regarding the trend of increasing off-label use, coupled with the uncertainty of the safety and efficacy of such use.²⁴⁻²⁶

Given the significant incentives available to pharmaceutical companies under the ODA, it is important to examine the pattern of utilization of these drugs and pricing strategy adopted by these companies and whether in reality their strategies coincide with the intent of ODA.

Study Objectives

This study aims to describe the utilization of orphan drugs by orphan use, non-orphan, on-label use, and off-label use, among a sample of FDA-approved orphan drugs between 2012-2014 and the cumulative price increases for each orphan drug over the same time period.

Methods Summary

There were 45 prescription medications identified with at least one FDA-approved orphan indication during 2012-14, including self-administered drugs and those administered in an outpatient clinical setting.²⁷ The cumulative percentage change in unit prices, from 2012 to 2014, was calculated for each drug's National Drug Code (NDC), using the Average Wholesale Prices (AWP) reported by REDBOOK.™ Only those NDCs having pricing data available for all three study years were included. For each drug, an average cumulative price change was calculated across all of the drug's NDCs.

Using the MarketScan® Commercial Claims and Encounters Databases (Truven Health Analytics, Inc.), a commercial insurance claims database, patients prescribed one of these 45 drugs were entered into the study if they had at least one outpatient pharmacy claim for one of the 45 orphan drugs and at least two outpatient medical claims. For each study year, based upon the FDA-approved drug labels in-force during

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2012 to 2014 and the ICD-9 diagnostic codes recorded in their outpatient claims data, patients were then classified as being either an “orphan patient”, a “non-orphan, on-label use patient”; or an “off-label use patient”. Patients were classified as an “orphan patient” if all of their outpatient claims for a given year were related to the drug’s orphan disease indication. Similarly, patients were classified as “non-orphan, on-label use patients” if all of their outpatient claims were related to the drug’s non-orphan, on-label indications. Finally, any patient having no orphan related or non-orphan, on-label related claims for a given year was classified as an “off-label use patient”. For those patients having a mix of outpatient medical claims types (orphan and/or non-orphan, diseases) the following decision rules were used to classify patients:

1. A patient was classified as an “orphan patient” if any one of their outpatient medical claims for a given year had a diagnostic code for an orphan disease of interest;
2. A patient was classified as a “non-orphan, on-label use patient” if they had no orphan disease related outpatient medical claim and at least one outpatient medical claim for a given year having a diagnosis for any of the drug’s FDA-approved, non-orphan indications, where applicable.

This conservative approach has the effect of providing the best chance for an orphan drug to demonstrate orphan or non-orphan on-label use in a given year.

For each study year, for each drug, the percentage of orphan use, non-orphan on-label use, and off-label use for each drug was calculated. The overall average (and standard deviation) utilization percentage for each type of utilization was calculated across all three study years. Pearson’s *r* was calculated to test for any significant correlations between the average change in prices and:

- the proportion of orphan use, averaged across three study years;
- the proportion of non-orphan, on-label use, averaged across the three study years;
- the proportion of off-label use, averaged across the three study years.

Finally, an ANOVA test was conducted to test for any statistically significant differences in price changes among the quartiles of orphan use; on-label use; and off-label use. The *a priori alpha* level was set at 0.05 for all tests of statistical significance. See Appendix for more details on methodology.

Findings

A total of 45 prescription medications were identified as having at least one FDA-approved, orphan indication in force during the entire 2012-2014 study period (Figure 3). Overall, the total number of patients with a prescription for at least one of these orphan drugs was: 240,634 patients; 216,834 patients; and 247,399 patients for 2012, 2013, and 2014, respectively. As shown in Table 5, across all study drugs, the average number of treated patients ranged from 26 patients per year (Nplate®) to 82,099 patients per year (Colcrys®).

For the entire sample, the average percentage of patients having at least one prescription for an orphan drug and at least one medical claim for a related orphan disease was 55.7 percent. The drug with the greatest average annual orphan utilization (98.4 percent) was Xiaflex®, where almost all patients prescribed this drug used to treat abnormal accumulations of collagen in the body, were diagnosed with an orphan condition. By contrast, only 0.3 percent of patients prescribed the gout drug, Colcrys®, had any evidence of being diagnosed with the orphan disease familial Mediterranean Fever. Similarly, of the 6,101 patients prescribed the Hepatitis B

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and HIV drug, Viread® during a typical year, only 6 patients per year (0.1 percent) had been diagnosed with an orphan condition.

With respect to other, non-orphan use, overall, 20.1 percent of patients had evidence of non-orphan, on-label use of these drugs. Non-orphan, on-label use was greater than 90 percent of the total utilization of the following orphan drugs: Humira® (90.2%); Viread® (90.5%); Remicade® (93.2%); and Herceptin® (96.6%). Overall, on-label use, be it orphan or non-orphan, accounted for 75.8 percent of the use of these orphan medications.

With respect to off-label use, 24.2 percent of use was for those patients lacking any claims data indicating a diagnosis of an orphan or an on-label non-orphan indication. As noted previously, for the purposes of this study, these patients were considered off-label patients. Off-label utilization ranged from only 1.2 percent, in the case of the breast cancer treatment, Herceptin®; to as high as 98.2 percent in the case of the pain medication, Gralise®.

Figure 1: Cumulative Percentage Change In Price By Average Percentage of Orphan Use (2012-2014)
(Pearson's $r = -0.4152$; $p = 0.0046$)

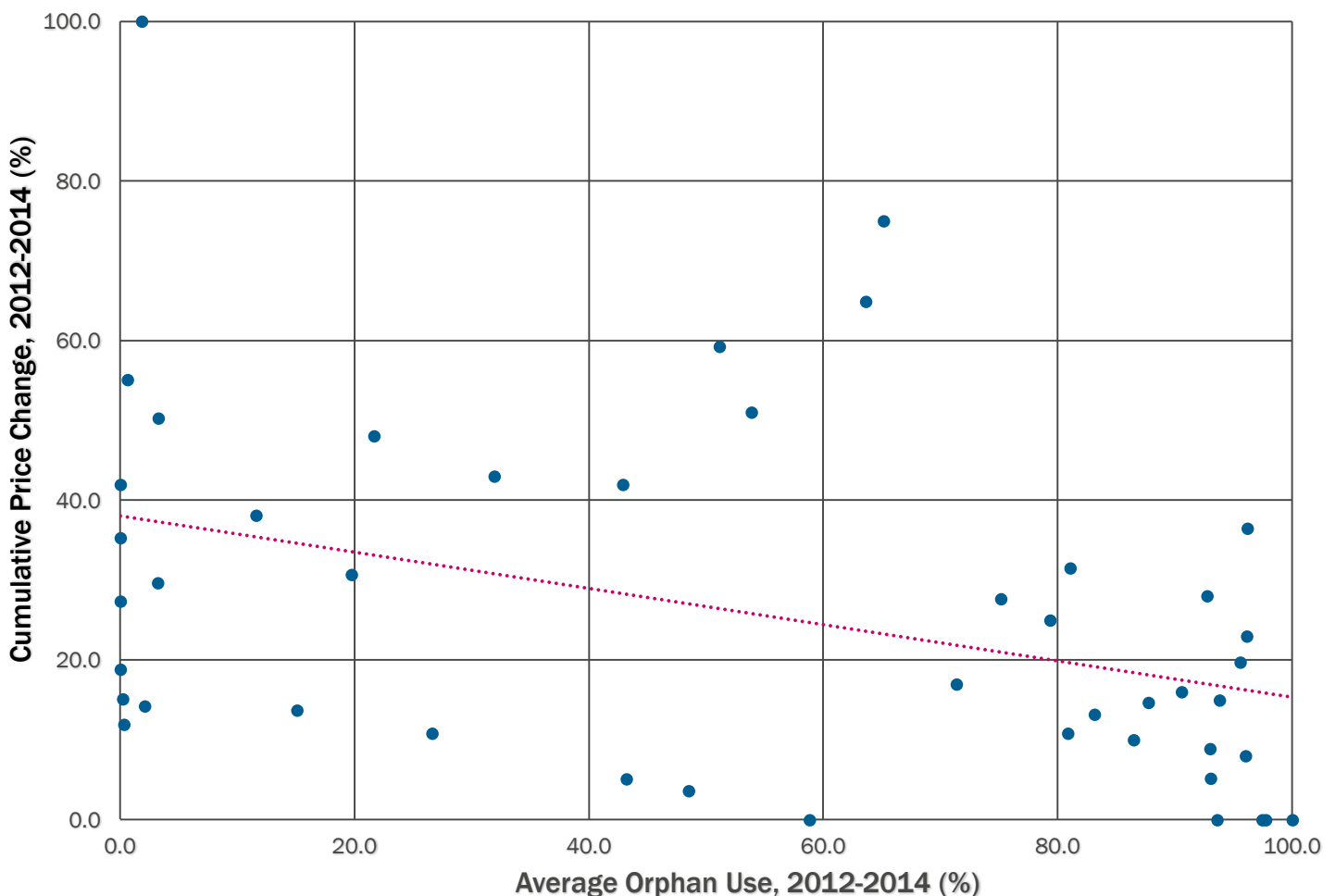
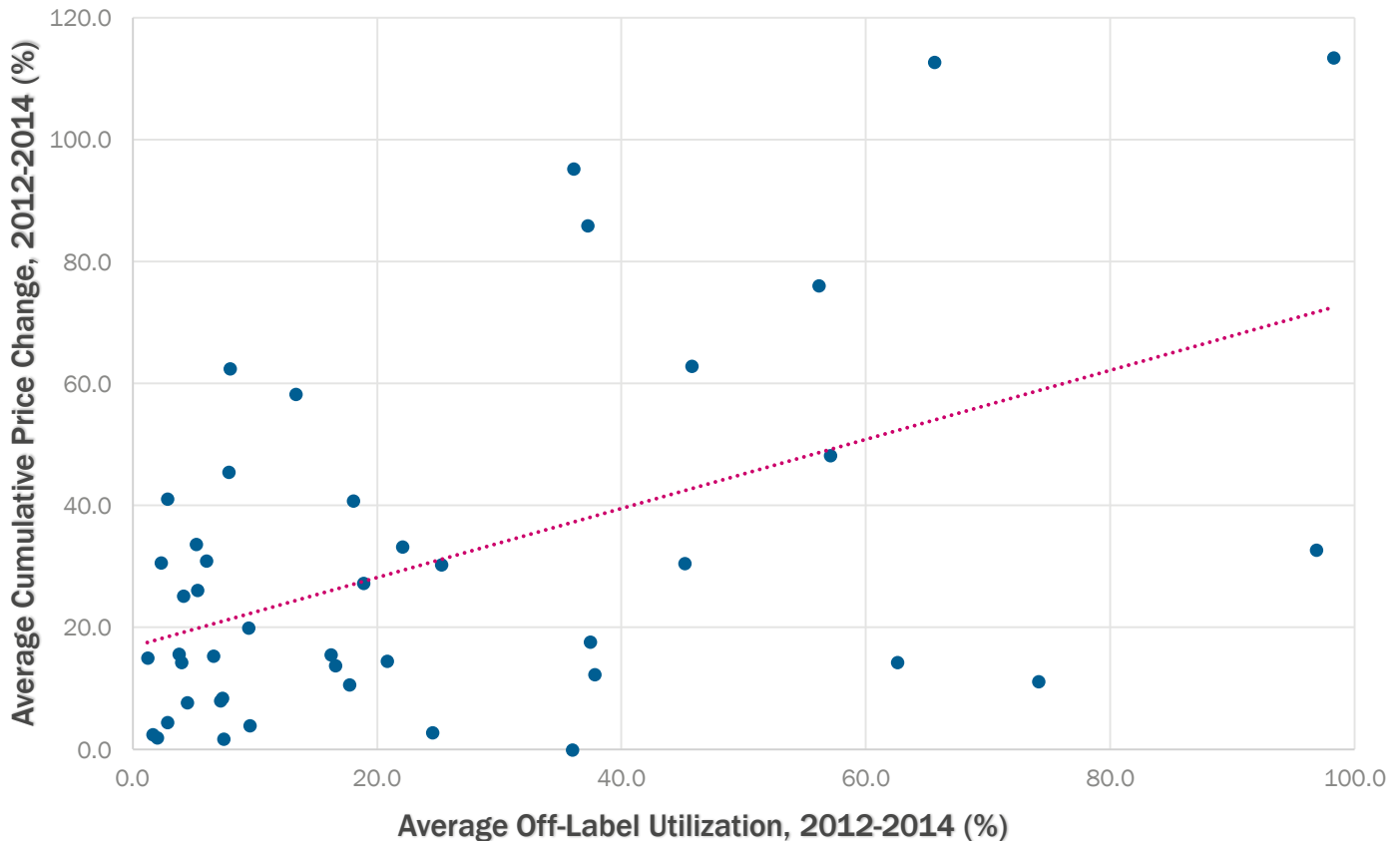


Figure 2: Cumulative Percentage Change In Price By Percentage of Off-Label Use (2012-2014)

(Pearson's $r = 0.4959$; $p = 0.0005$)



On average, the price for this sample of 45 orphan drugs increased by 30.6 percent during the three-year study period. As shown in Table 5, seven drugs posted price increases of less than 5 percent during the three-year study period, with Makena® posting no price increase at all. However, the manufacturers of other drugs in the sample, including Gralise®, Horizant®, Sabril®, Adcirca®, Banzel®, Zirgan®, and Humira® increased their product’s price in excess of 60 percent over the span of just three years.

The study found a statistically significant, negative correlation between orphan use and pricing. As shown in Figure 1, as orphan utilization increased, the cumulative change in

price decreased, suggesting that non-orphan use may be contributing to price increases.

The study also found a statistically significant correlation between off-label use and pricing. As shown in Figure 2, as off-label use increased among the study drugs the cumulative change in a drug’s price increased as well, suggesting that off-label use may be factoring into drug companies pricing decisions.

Finally, the study failed to find a statistically significant correlation between non-orphan, on-label utilization and pricing ($p=0.5717$). This lack of a statistically significant correlation may be explained by the fact that almost two-thirds of the drugs studied (30 of 45 drugs) either did not

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Table 1: Analysis of Variance (ANOVA) Results: Orphan Utilization
($F= 3.17$; $p= 0.0344$)

Quartile	Average Annual Orphan Utilization	Sample Size (drugs)	Average (SD) Cumulative Price Change (%)
—	Overall Sample of Orphan Drugs	45	30.6 (29.0)
1	Subgroup of drugs having 0-19.7% Average	11	42.4 (38.1)
2	Subgroup of drugs having 19.8-62.7% Average	11	43.4 (28.3)
3	Subgroup of drugs having 62.8-92.6% Average	11	23.3 (24.3)
4	Subgroup of drugs having 92.7-100% Average	12	14.7 (12.1)
p-Value:			0.0344

Mean Orphan Use (SD) for the overall sample was 53.2% (38.3)

have any evidence of on-label use or were approved for orphan indications only and therefore, had no on-label use. This may have resulted in too small of a sample to detect any meaningful correlation.

With respect to the results from the ANOVA analysis, as summarized above, the sample of 45 orphan drugs was grouped by quartile of orphan use. The drugs having little to no orphan utilization (0-19.7 percent) increased their prices, on average, by 42.4 percent over the course of the three study years. However, those orphan drugs used almost exclusively for their orphan disease (92.7-100 percent) increased their prices by only 14.7 percent from 2012 to 2014.

For the second ANOVA analysis, the sample of orphan drugs was grouped by quartile of off-label

use (Table 2). Those drugs having little-to-no off-label use, increased their prices the least over the three-year period, 15.9 percent; however, those drugs with off-label utilization exceeding 37.2 percent, increased their prices by 51.5 percent during the study period.

Results from these ANOVA analyses suggest that the differences in pricing among the 45 drugs studied, cannot be explained by mere chance alone and may be influenced by the degree and type of drug utilization, be it orphan use or off-label use. As with the correlation studies, no significant findings were detected for FDA-approved, non-orphan, on-label use; however, this may be a reflection of the paucity of on-label use data available, as previously noted.

Table 2: Analysis of Variance (ANOVA) Results: Off-Label Utilization
($F= 3.70$; $p= 0.0191$)

Quartile	Average Annual Off-Label Utilization	Sample Size (drugs)	Average (SD) Cumulative Price Change (%)
—	Overall Sample of Orphan Drugs	45	30.6 (29.0)
1	Subgroup of drugs having 0-5.1% Average	10	15.9 (13.0)
2	Subgroup of drugs having 5.2-16.1% Average	12	26.2 (20.7)
3	Subgroup of drugs having 16.2-37.1% Average	11	25.9 (26.3)
4	Subgroup of drugs having 37.2-100% Average	12	51.5 (38.2)
p-Value:			0.0191

Mean Off-Label Use (SD) for the overall sample was 24.2% (25.4)

Conclusion

Since its inception in 1983, the ODA has been widely regarded as a major success. It has proven to be instrumental in facilitating the development of more than 500 drugs to treat rare diseases that otherwise might not have been developed. With many more medications still in development pipelines, the ODA promises to be an important tool in the ongoing fight to treat the 6,000 - 7,000 rare diseases that remain with few, if any, treatment options.

However, not all orphan drugs exclusively target rare conditions. As this study demonstrates, only a handful of the 45 orphan drugs studied were used exclusively for the orphan disease they were developed to treat. Many medications on the market today, in addition to treating the rare disease for which they are indicated, may also be used on-label or off-label to treat other, more widely-prevalent, non-orphan conditions. Over 40 percent of the utilization of the orphan drugs in this study was for non-orphan indications. Thus, orphan drugs have become a lucrative business opportunity for drug makers.

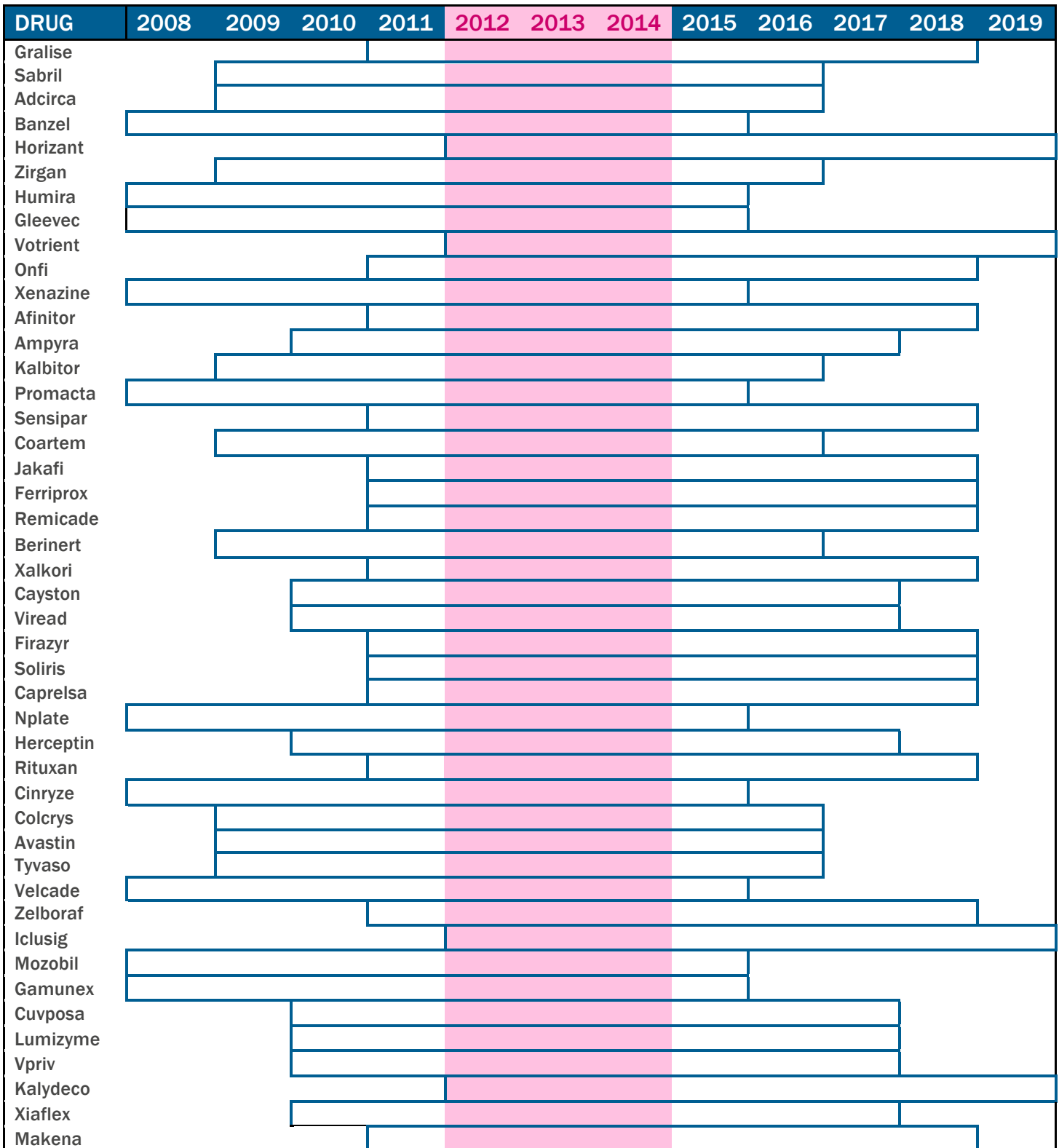
Although much attention has been paid in recent months to the widespread economic impact caused by certain high-priced, non-orphan drugs like Sovaldi®, Daraprim®, and a growing list of specialty medications, the economic impact of orphan drugs needs to be recognized as well. Orphan drugs, long-thought to be treating so few patients each year that they did not present a reimbursement challenge for payers, are now being more closely scrutinized by public and private payers.²⁸ The days of viewing orphan drugs as having limited impacts on payer's pharmacy budgets are ending.^{29,30}

To be clear, while, there are no regulatory or legal restrictions preventing pharmaceutical companies from expanding the use of their orphan drugs, either by gaining additional FDA approvals or by off-label usage; some authors have suggested that some drug makers appear to be “gaming the system” when it comes to the ODA.³¹ Drug companies do accrue a number of benefits, outlined previously, by virtue of developing their drug in an orphan indication and some have called for drug makers to have to “payback” the United States taxpayers for these benefits once their orphan drug's utilization or annual revenues reach certain threshold levels.³¹ In addition, the FDA needs to better challenge drug companies' ability to target their orphan drug development to a subset of patients diagnosed with the disease in order to remain under the 200,000 patient cut-off set for orphan eligibility.³¹ As the prices for these agents continue to climb, it is becoming increasingly urgent that the original intent of the Orphan Drug Act be restored. A proper balance has to be struck between ensuring that the incentives remain for those firms focused on developing these very important, and much-needed orphan disease therapies; while not allowing for the Act to be exploited purely for financial gain.

Appendix

Figure 3: Orphan Exclusivity Periods by Drug

■ study period



Appendix

Table 3: Listing of Orphan Indications and Corresponding ICD-9 Codes

Brand Name	Orphan Indication(s)	ICD-9 Code(s)
Gralise	Management of post-herpetic neuralgia	053.10-.14; 053.19
Sabril	Treatment of infantile spasms in children less than 2 years-old	345.60; 345.61
Adcirca	Treatment of pulmonary arterial hypertension	416.0
Banzel	Adjunctive therapy of seizures associated with Lennox-Gastaut Syndrome	345.40-.41; 345.50-.51; and 345.80-.81
Horizant	Management of post-herpetic neuralgia	053.10-.14; 053.19
Zirgan	Treatment of acute herpetic keratitis (dendritic ulcers)	054.40-.44; 054.49
Humira	Treatment of: 1) polyarticular juvenile idiopathic arthritis; 2) pediatric Crohn's Disease in patients aged 6-16 years-old (2014)	714.30-.31; 550.0-.2; 550.9
Gleevec	Treatment of: 1) metastatic dermatofibrosarcoma protuberans; 2) mastocytosis; 3) myelodysplastic/myeloproliferative disorders; 4) hypereosinophilic syndrome; 5) chronic eosinophilic leukemia; 6) Ph+ acute lymphoblastic leukemia; 7) gastrointestinal stromal tumors	238.1; 151.9; 152.9; 204.00-204.02
Votrient	Treatment of advanced soft tissue sarcomas	171.0; 171.2-9
Onfi	Treatment of seizures associated with Lennox-Gastaut Syndrome in children 2 years-old or older	345.40-.41; 345.50-.51; and 345.80-.81
Xenazine	Chorea associated with Huntington's Disease	333.4
Afinitor	Treatment of: 1) subependymal giant cell astrocytoma associated with tuberous sclerosis; 2) angiomyolipoma; 3) progressive neuroendocrine tumors of pancreatic origin	157.4; 191.9; 223.0
Ampyra	Treatment to improve walking in multiple sclerosis patients	340
Kalbitor	Treatment of acute attacks of hereditary angioedema in patients aged 16 year-old or older.	277.6
Promacta	Treatment of: 1) thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura; 2) aplastic anemia (2014)	287.31; 287.33; 287.5; 284.01-.09; 284.81-.89; 284.9
Sensipar	Treatment of hypercalcemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy	237.40; 252.00-.02; 252.08; 275.42
Coartem	Treatment of malaria due to Plasmodium falciparum	08.40; 08.45; 08.46
Jakafi	Treatment of: 1) primary myelofibrosis; 2) polycythemia vera; 3) essential thrombocythemia myelofibrosis	238.4; 238.71; 238.76; 289.83
Ferriprox	Treatment of transfusional iron overload, due to thalassemia syndromes	275.01-.03; 275.09
Remicade	Treatment of ulcerative colitis in patients aged 6 years-old or older	556.0-6; 556.8; 556.9
Berinert	Treatment of acute attacks of hereditary angioedema	277.6
Xalkori	Locally advanced or metastatic non-small cell lung cancer	162.0; 162.2-5; 162.8; 162.9

Table continued on page 12



Appendix

Brand Name	Orphan Indication(s)	ICD-9 Code(s)
Cayston	To improve respiratory function in cystic fibrosis patients	277.00-.03; 277.09
Viread	Treatment of pediatric HIV infection in patients 12-17 years-old	042; V08; V01.79; 079.53; 795.71
Firazyr	Treatment of acute attacks of hereditary angioedema	277.6
Soliris	Treatment of: 1) atypical hemolytic uremic syndrome; 2) paroxysmal nocturnal hemoglobinuria to reduce hemolysis	283.11; 283.2; 283.9
Caprelsa	Treatment of advanced or metastatic medullary thyroid cancer	193
Nplate	Treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura	287.31; 287.33; 287.5
Herceptin	HER2+ metastatic or gastroesophageal adenocarcinoma	151.0; 151.9
Rituxan	Treatment of: 1) CD20+ chronic lymphocytic leukemia; 2) Wegener's Granulomatosis; 3) microscopic angiitis	204.10-12; 446.0; 446.4
Cinryze	Prophylaxis of angioedema attacks in hereditary angioedema	277.6
Colcryl	Treatment of familial Mediterranean Fever	277.31
Avastin	Treatment of: 1) glioblastoma multiforme; 2) renal cell carcinoma; 3) ovarian cancer; 4) fallopian tube cancer; 5) primary peritoneal cancer	189.0; 189.1; 189.9; 191.0; 191.1; 191.2-9
Tyvaso	Treatment of pulmonary arterial hypertension	416.0
Velcade	Treatment of: 1) mantle cell lymphoma; 2) multiple myeloma (first-line)	200.40-48; 203.00-02; 203.10-12; 203.80-82
Zelboraf	Treatment of BRAFV600E+ advanced or metastatic melanoma	172.0-9
Iclusig	Treatment of: 1) chronic myeloid leukemia; 2) Ph+ acute lymphoblastic leukemia	204.00-02; 205.10-12
Mozobil	Mobilization of hematopoietic stem cells for autologous transplantation in lymphoma and multiple myeloma patients	202.80-88; 203.00-02; 203.10-12; 203.80-82
Gamunex	Treatment of chronic inflammatory demyelinating polyneuropathy	357.81; 357.89
Cuvposa	Treatment of chronic drooling in neurologic conditions associated with excessive drooling	343.9; 527.7
Lumizyme	Treatment of late-onset Pompe Disease	271.0; 271.9
Vpriv	Treatment of Type 1 Gaucher Disease	272.7; 272.9
Kalydeco	Treatment of cystic fibrosis in patients aged 6 years-old and older	277.00-03; 277.09
Xiaflex	Treatment of: 1) Peyronie's Disease; 2) Dupuytren's Contracture	607.85; 728.6
Makena	To reduce the risk of preterm birth with singleton pregnancy	644.00; 644.03; 644.20-21; 646.30-31; 646.33; V23.41; V13.21

Appendix

Table 4: Listing of FDA-Approved, Non-Orphan Indications and Corresponding ICD-9 Codes

Brand Name	Non-Orphan Indication(s)	ICD-9 Code(s)
Sabril	Refractory complex seizures, with or without secondary generalization	354.00; 345.01; 345.10;345.11; 345.2; 345.3; 345.40; 345.11; 345.60; 345.61; 345.80; 345.81; 345.90; 345.91
Horizant	Moderate-to-severe restless leg syndrome	333.94
Humira	Rheumatoid arthritis; Psoriatic Arthritis; Ankloysing Spondylitis; Crohn's Disease; Psoriasis; Ulcerative Colitis	714.0; 714.9; 696.0; 720.0; 720.9; 555.0-555.2; 555.9; 696.1; 556.0-556.6; 556.8; 556.9
Gleevec	Philadelphia Chromosome Positive Chronic Myelogenous Leukemia and Acute Lymphoplasic Leukemia	205.10-205.12; 205.90-205.92; 204.00-204.02; 204.90-204.92
Votrient	Renal Cell Carcinoma	189.0; 189.1
Afinitor	Hormone Receptor Positive; HER2 Negative Breast Cancer; Renal Cell Carcinoma	174.0-174.6; 174.8; 174.9; 189.0; 189.1
Promacta	Thrombocytopenia with Chronic Hepatitis C	070.41; 070.44; 070.51; 070.54; 070.70; 070.71;
Sensipar	Hyperparathyroidism associated with Chronic Kidney Disease; Hypercalcemia associated with Parathyroid Carcinoma	585.1-585.6; 585.9; 194.1
Remicade	Crohn's Disease; Ulcerative Colitis; Rheumatoid Arthritis; Ankylosing Spondylitis; Psoriatic Arthritis; Psoriasis	714.0; 714.9; 696.0; 720.0; 720.9; 555.0-555.2; 555.9; 696.1; 556.0-556.6; 556.8; 556.9
Viread	Chronic Hepatitis B Infection; Combination therapy to treat HIV1 Infection in Adults	070.20-070.23; 070.30-070.33; 070.42; 070.52; 070.6; 070.9; 042; V08; V01.79; 079.53; 795.71
Herceptin	HER2 Positive Breast Cancer	174.0-174.6; 174.8; 174.9
Rituxan	Non-Hodgkins' Lymphoma; Rheumatoid Arthritis	202.80; 714.0; 714.9
Colcrys	Gout flares	274.00-03; 274.10; 274.11; 274.19; 274.81; 274.82; 274.89; 274.9
Avastin	Metastatic Colo-Rectal Cancer; Non-Squamous Non-Small Cell Lung Cancer; HER2 Negative Breast Cancer (removed May 2012); Cervical Cancer	153.0-153.4; 153.6-153.9; 154.0; 154.1; 162.0; 162.2-162.5; 162.8; 162.9; 174.0-174.6; 174.8; 174.9; 180.0; 180.1; 180.8; 180.9
Gamunex	Primary Humoral Immunodeficiency; Idiopathic Thrombocytopenia Purpura	279.00-279.06; 279.09; 279.3; 279.9; 287.31

Appendix

Table 5: Description of Analytical Sample by Orphan Drug (2012-2014)

Orphan Drug	Average Cumulative Price Change, 2012-2014 (%)	Average Annual Utilization, 2012-2014 (%):			Average Annual Sample Size (Patients)
		Orphan Use	Non-Orphan Use	Off-Label Use	
Gralise	113.5	1.8	0.0	98.2	5703
Horizant ¹	112.8	1.1	33.4	65.6	1640
Sabril	95.3	42.1	21.9	36.0	162
Adcirca	86.0	62.8	0.0	37.2	855
Banzel	76.1	43.9	0.0	56.1	483
Zirgan	62.9	54.3	0.0	45.7	4672
Humira	62.5	1.9	90.2	7.9	43466
Gleevec	58.3	23.1	63.6	13.3	2575
Xenazine	48.2	43.0	0.0	57.0	260
Votrient	45.5	34.9	57.3	7.8	630
Ampyra	41.1	97.2	0.0	2.8	3308
Afinitor	40.8	9.3	72.7	18.0	1217
Promacta	33.7	84.5	10.3	5.2	303
Kalbitor	33.3	78.0	0.0	22.0	32
Coartem	32.7	3.2	0.0	96.8	306
Jakafi	31.0	94.0	0.0	6.0	177
Remicade	30.7	4.5	93.2	2.3	28938
Onfi	30.5	54.9	0.0	45.1	2026
Ferriprox	30.3	74.8	0.0	25.2	29
Berinert	27.3	81.1	0.0	18.9	57
Sensipar	26.1	19.8	74.9	5.2	4363
Xalkori	25.2	95.9	0.0	4.1	182
Viread	20.0	0.1	90.5	9.5	6101
Firazyr	17.7	62.6	0.0	37.4	96
Caprelsa	15.7	96.2	0.0	3.8	34
Nplate	15.6	83.8	0.0	16.2	26
Zelboraf	15.4	93.4	0.0	6.6	242
Herceptin	15.1	2.2	96.6	1.2	6771
Rituxan	14.5	12.5	66.7	20.8	9274
Cayston	14.3	96.0	0.0	4.0	801
Cuvposa	14.3	37.5	0.0	62.5	167
Cinryze	13.8	83.5	0.0	16.5	79
Colcrys	12.3	0.3	61.9	37.8	82099
Avastin	11.2	7.8	18.1	74.1	19033
Tyvaso	10.7	82.3	0.0	17.7	87
Soliris	8.4	92.7	0.0	7.3	200
Iclusig ²	8.0	92.9	0.0	7.1	31
Velcade	7.7	95.6	0.0	4.4	2021
Kalydeco	4.5	97.2	0.0	2.8	121
Mozobil	4.0	90.4	0.0	9.6	34
Gamunex	2.8	22.6	52.9	24.5	3341
Xiaflex	2.5	98.4	0.0	1.6	1387
Vpriv	2.0	98.0	0.0	2.0	85
Lumizyme ³	1.8	92.6	0.0	7.4	47
Makena	0.0	64.1	0.0	35.9	1493

1. The cumulative price change is based on changes in the unit price for NDC #00173-0806-01 & #53451-0101-01.

2. As ICLUSIG® was not approved by the FDA until December, 2012 it was included in the study; however, its pricing and utilization data were from 2013 to 2014 only.

3. Includes patients prescribed MYOZYME®

Appendix

Table 6: Orphan Drug Utilization by Type and Year (2012-2014)

Drug	Average Cumulative Price Change, 2012-2014 (%)	Orphan Use (%)			Non-Orphan Use (%)			Off-Label Use (%)		
		2012	2013	2014	2012	2013	2014	2012	2013	2014
Gralise	113.5	2.3	1.5	1.5	0.0	0.0	0.0	97.7	98.5	98.5
Horizant ¹	112.8	1.2	0.9	1.0	37.9	33.8	28.4	60.9	65.3	70.5
Sabril	95.3	42.3	40.1	43.8	20.6	22.3	22.9	37.1	37.6	33.3
Adcirca	86.0	67.2	61.1	60.2	0.0	0.0	0.0	32.8	38.9	39.8
Banzel	76.1	41.4	45.7	44.7	0.0	0.0	0.0	58.6	54.3	55.3
Zirgan	62.9	56.1	54.6	52.2	0.0	0.0	0.0	43.9	45.4	47.8
Humira	62.5	1.7	1.6	2.4	89.2	90.6	90.9	9.2	7.9	6.7
Gleevec	58.3	24.9	25.2	19.3	62.1	61.1	67.6	13.0	13.7	13.1
Xenazine	48.2	45.2	44.6	39.1	0.0	0.0	0.0	54.8	55.4	60.9
Votrient	45.5	39.0	33.3	32.4	52.7	59.2	60.0	8.3	7.5	7.6
Ampyra	41.1	97.0	97.5	97.2	0.0	0.0	0.0	3.0	2.5	2.8
Afinitor	40.8	8.4	8.8	10.7	72.7	74.9	70.4	18.8	16.3	18.9
Promacta	33.7	87.5	76.4	89.5	8.5	16.9	5.5	3.9	6.7	4.9
Kalbitor	33.3	78.8	73.3	81.8	0.0	0.0	0.0	21.2	26.7	18.2
Coartem	32.7	5.7	1.8	2.2	0.0	0.0	0.0	94.3	98.2	97.8
Jakafi	31.0	96.0	93.8	92.2	0.0	0.0	0.0	4.0	6.2	7.8
Remicade	30.7	5.7	6.3	1.6	92.2	91.3	96.0	2.1	2.4	2.4
Onfi	30.5	55.2	54.8	54.5	0.0	0.0	0.0	44.8	45.2	45.5
Ferriprox	30.3	73.9	74.1	76.3	0.0	0.0	0.0	26.1	25.9	23.7
Berinert	27.3	87.3	69.8	86.4	0.0	0.0	0.0	12.7	30.2	13.6
Sensipar	26.1	19.8	20.3	19.4	74.7	74.1	75.9	5.4	5.6	4.7
Xalkori	25.2	96.8	95.6	95.2	0.0	0.0	0.0	3.2	4.4	4.8
Viread	20.0	0.1	0.1	0.0	89.8	90.8	90.9	10.2	9.1	9.1
Firazyr	17.7	56.3	66.0	65.6	0.0	0.0	0.0	43.8	34.0	34.4
Caprelsa	15.7	95.2	96.8	96.7	0.0	0.0	0.0	4.8	3.2	3.3
Nplate	15.6	75.0	91.7	84.8	0.0	0.0	0.0	25.0	8.3	15.2
Zelboraf	15.4	97.4	94.3	88.6	0.0	0.0	0.0	2.6	5.7	11.4
Herceptin	15.1	2.2	2.2	2.4	96.8	96.5	96.4	1.0	1.3	1.3
Rituxan	14.5	12.2	12.5	12.8	69.2	66.0	64.9	18.6	21.5	22.3
Cayston	14.3	96.1	95.7	96.3	0.0	0.0	0.0	3.9	4.3	3.7
Cuvposa	14.3	40.2	38.1	34.1	0.0	0.0	0.0	59.8	61.9	65.9
Cinryze	13.8	83.5	83.8	83.1	0.0	0.0	0.0	16.5	16.3	16.9
Colcrys	12.3	0.2	0.3	0.3	62.0	61.1	62.8	37.8	38.6	36.9
Avastin	11.2	6.9	6.3	10.2	20.6	17.4	16.3	72.4	76.3	73.5
Tyvaso	10.7	83.0	81.0	82.9	0.0	0.0	0.0	17.0	19.0	17.1
Soliris	8.4	92.4	91.4	94.2	0.0	0.0	0.0	7.6	8.6	5.8
Iclusig ²	8.0	–	90.7	95.0	–	0.0	0.0	–	9.3	5.0
Velcade	7.7	96.7	95.3	94.7	0.0	0.0	0.0	3.3	4.7	5.3
Kalydeco	4.5	97.2	96.5	97.9	0.0	0.0	0.0	2.8	3.5	2.1
Mozobil	4.0	95.2	88.6	87.5	0.0	0.0	0.0	4.8	11.4	12.5
Gamunex	2.8	21.7	22.3	23.7	52.9	53.0	52.9	25.4	24.7	23.4
Xiaflex	2.5	98.6	98.6	98.1	0.0	0.0	0.0	1.4	1.4	1.9
Vpriv	2.0	99.0	100.0	95.1	0.0	0.0	0.0	1.0	0.0	4.9
Lumizyme	1.8	96.1	93.5	88.1	0.0	0.0	0.0	3.9	6.5	11.9
Makena	0.0	66.1	63.2	62.9	0.0	0.0	0.0	33.9	36.8	37.1

1. The cumulative price change is based on changes in the unit price for NDC #00173-0806-01 & #53451-0101-01.
2. As ICLUSIG® was not approved by the FDA until December, 2012 it was included in the study; however, its pricing and utilization data were from 2013 to 2014 only.
3. Includes patients prescribed MYOZYME®



Methods

Data sources. For this retrospective, cross-sectional, administrative claims database study, two data sources were used. All drug unit price data were extracted from the REDBOOK™ (Truven Health Analytics, Inc.). Only the AWP data listed in the 30 Sep 2015 edition were used. For the creation of the key variables of interest, namely, the orphan utilization, on-label utilization and off-label utilization averages, all medical and pharmacy claims data were extracted from the 2012, 2013, and 2014 MarketScan® Commercial Claims and Encounters Databases (Truven Health Analytics, Inc.). We investigated the utilization of the study drugs in the inpatient setting and found very few patients. Thus, only claims stored in the outpatient prescription drugs and outpatient services files were used in this study.

Inclusion/exclusion criteria. Using the FDA’s online orphan drug search function,³² we identified 80 prescription medications having at least one FDA-approved, orphan indication in effect during the study time period of 01 Jan 2012 to 31 Dec 2014. We excluded any vaccines, implants, agents used for diagnostic purposes, and hemophilia agents. The orphan indications of two drugs (Krystexxa® and Xiaifaxan®) could not be operationalized reliably using only claims data and were excluded. For example, Krystexxa® is indicated for the treatment of chronic gout refractory to conventional therapy.³³ Although claims data can indicate if a patient is diagnosed with chronic gout, it does not indicate if that patient has become refractory to conventional therapy. Given this study focuses on orphan drugs only and as many of these agents are rarely used, we conducted an initial exploratory analysis of the remaining 72 drugs. Based on this exploratory analysis we arrived at a final analytical sample of 45 orphan drugs, including self-administered drugs and those administered in an outpatient clinical setting.

Variable descriptions. “Average Cumulative Price Change” was calculated for each drug’s NDC using the AWP unit price data from the September 2015 edition of REDBOOK™. The AWP unit price in effect on 01 Jan 2012 for a given NDC was subtracted from the AWP unit price in effect on 31 Dec 2014 and divided by the AWP unit price in effect on 01 Jan 2012, with the resulting fraction multiplied by 100. For each drug, to calculate the Average Cumulative Price Change for that drug the cumulative price changes for all NDCs were then averaged.

“Average Percent Orphan Use”. This variable was created by first compiling the orphan indications, collected from the FDA approved package inserts, for each of the 45 orphan drugs.³⁴ Each orphan indication was then mapped to the relevant ICD-9 code(s) (Table 3).³⁵ Next, any patient having at least one outpatient pharmacy prescription, or for those drugs administered mainly in the office-setting, having at least two medical claims for the drug’s administration were extracted from the 2012, 2013, and 2014 MarketScan® Commercial Claims and Encounters Databases. Any patient having claims for more than one study drug in a given year were excluded. This final pool of patients was then sub-grouped by study drug to form 45 subgroups of patients.

An indicator variable was then created for each of the 45 subgroups of patients, to identify those patients who had at least one outpatient medical claim with one of the first two diagnostic fields containing one of the relevant, orphan disease ICD-9 codes. These patients were then considered “orphan patients,” that is, those who had at least some evidence of having been diagnosed with one of the orphan diseases of interest at least once during a given study year. Furthermore, for those drugs having an orphan indication which explicitly applied to a particular age range, for example, Humira’s orphan indication in pediatric Crohn’s Disease is restricted for use in patients aged 6-16 year-old, only those patients diagnosed with Crohn’s Disease and meeting that age requirement were classified as “orphan patients”.

Appendix

Lastly, as some drugs received additional orphan indications during the study period, patients diagnosed during the year of FDA-approval of an additional orphan indication, or diagnosed thereafter, were classified as “*orphan patients*.” For example, Promacta® received FDA approval for the treatment of chronic immune (idiopathic) thrombocytopenia purpura (ITP) in 2008 and later, for aplastic anemia in 2014. Only patients diagnosed with aplastic anemia during 2014 were added to the pool of ITP patients and classified as “*orphan patients*”. In a similar manner, for those drugs having multiple orphan indications, if one of those orphan exclusivity periods expired during the study period, those orphan indications were considered non-orphan, on-label use for the year(s) following expiration of the exclusivity period. For each drug, for each study year, the total number of orphan patients was then divided by the total sub-group of patients (i.e, all patients prescribed the drug that year) and the resulting fraction multiplied by 100 to yield the percent orphan use for that drug for that year. Each annual estimate of orphan utilization for each drug was then averaged across all three study years. The standard deviation was also calculated.

“*Percent Non-Orphan, On-Label Use*”. In a similar manner as the orphan use variable, an indicator variable was created for each of the 45 drug subgroups of patients, to identify those patients who had at least one outpatient medical claim with one of the first two diagnostic fields containing one of the relevant, non-orphan, on-label disease ICD-9 codes (Table 4). Any age restrictions attached to an on-label indication were included in the same manner as age restrictions for the orphan indications. For each drug, for each study year, the total number of on-label patients was then divided by the total sub-group of patients (i.e, all patients prescribed the drug that year) and the resulting fraction multiplied by 100 to yield the percent non-orphan, on-label use for that drug for that year. Each annual estimate of non-orphan, on-label utilization for each drug was then averaged across all three study years. The standard deviation was also calculated.

“*Percent Off-Label Use*”. Finally, those patients having at least one prescription for one of the 45 study drugs of interest but no medical claim having a relevant orphan disease ICD-9 code or non-orphan, on-label disease ICD-9 code appearing in one of the first two diagnostic fields were considered “off-label patients.”

For each drug, for each year, the total number of off-label patients was then divided by the total sub-group of patients (i.e, all patients prescribed the drug that year) and the resulting fraction multiplied by 100 to yield the percent off-label use for that drug for that year. Each annual estimate of off-label utilization for each drug was then averaged across all three study years. The standard deviation was also calculated.

Patient Classification Decision-Rules. For those patients having a mix of outpatient claims types in a given year, the following decision rules were used:

1. A patient was classified as an “orphan patient” if any one of their outpatient medical claims for a given year had a diagnostic code for an orphan disease of interest (Table 3);
2. A patient was classified as a “non-orphan, on-label use patient” if they had no orphan disease related outpatient medical claim and at least one outpatient medical claim for a given year having a diagnostic code for any of the drug’s FDA-approved, non-orphan indications, where applicable (Table 4);

Analytical approach. All data management and analysis activities were performed using SAS Enterprise Guide 6.1. For all tests of significance, the a priori alpha level was set at 0.05. Pearson’s r was calculated to test for any significant correlations between the two variables of interest, utilization and price change. ANOVA analyses were performed to compare quartiles of utilization and price changes.

Related Topic



1 The United States Food and Drug Administration. The Orphan Drug Act, relevant excerpts.

<http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm364750.htm>

2 Electronic Code of Federal Regulations. 21.316 Subpart C: Designation of an Orphan Drug. <http://www.ecfr.gov/cgi-bin/text>

<http://www.ecfr.gov/cgi-bin/text?id=c:ecfr&SID=238362420de6b80c19b2a9c44b73a843&rgn=div6&view=ext&node=21:5.0.1.1.63&idno=21>

3 Seoane-Vazquez E, Rodriguez-Monguio R, Szeinbach SL, et al. Incentive for Orphan Drug Research and Development in the United States. *Orphanet: The Journal of Rare Disease* 2008; 3:33. doi:10.1186/1750-1172-3-33

4 Kwok AK, Koenigbauer FM. Incentives to Repurpose Existing Drugs for Orphan Indications. *ACS Medicinal Chemistry Letters* 2015; 6: 828-830.

5 Kinch MS, Merkel J, and Umlauf S. Trends in Pharmaceutical Targeting of Clinical Indications: 1930-2013. *Drug Discovery Today* Nov 2014; 19(11): 1682-1685.

6 Thorat C, Xu K, Freeman SN, et al. What the Orphan Drug Act Has Done Lately for Children with Rare Diseases: A 10-Year Analysis. *Pediatrics* 2012; 129: 516-521.

7 Valentine JE and Clissold DB. A Year in Review: Important Intel Gleaned from CDER Report on New Drug Approvals. *The FDA Law Blog*; 27 December 2015.

http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2015/12/a-year-in-review-important-intel-gleaned-from-cder-report-on-new-drug-approvals.html

8 Sharma A, Jacobs A, Tandon M., et al. Orphan Drug: Development Trends and Strategies. *Journal of Pharmacy and Bioallied Sciences* 2010; 2(4): 290-299.

9 Phillips MI. Big Pharma's New Model in Orphan Drugs and Rare Diseases. *Expert Opinion on Orphan Drugs* 2013; 1(1): 1-3

<http://dx.doi.org/10.1517/21678707.2013.752128>

10 Fagnan DE, Gromatzky AA, Stein RM, et al. Financing Drug Discovery for Orphan Diseases. *Drug Discovery Today* May 2014; 19(5): 533-538.

11 Thomson-Reuters. *The Economic Power of Orphan Drugs*, 2012.

<http://www.thomsonreuters.com/content/dam/openweb/documents/pdf/pharma-life-sciences/white-paper/1001450.pdf>

12 Meekings KN, Williams CSM, Arrowsmith JE, et al. Orphan Drug Development: An Economically Viable Strategy for Biopharma R&D. *Drug Discovery Today* Jul 2012; 17(13-14): 660-664.

13 Pulsinelli GA. The Orphan Drug Act: What's Right With It? *Santa Clara High-Technology Law Journal* 1999; 15(2): 299-345.

14 Haffner ME, Torrent-Farnell J, and Maher PD. Does Orphan Drug Legislation Really Answer the Needs of Patients? *The Lancet* 2008; 371(9629): 2041-2044.

15 Wellman-Labadie O and Zhou Y. The US Orphan Drug Act: Rare Disease Research Stimulator or Commercial Opportunity? *Health Policy* 2010; 95(2-3): 216-228.

16 Almashat S, Sorscher S, and Knievel S. House Orphan Drug Proposal: A Windfall for Pharma, False 'Cure' for Patients. *Public Citizen* 2015.

<http://www.citizen.org/documents/2289.pdf>

17 Burns TM, Smith GA, Allen JA, et al. Editorial By Concerned Physicians: Unintended Effect of the Orphan Drug Act on the Potential Cost of 3,4-Diaminopyridine. *Muscle Nerve* 2016; 53: 165-168.

18 Tavernise S. Patients Fear Spike in Price of Old Drugs. *The New York Times*. 22 Dec 2015. <http://nyti.ms/22oTZ02>

19 Cote A, Keating B. What is Wrong with Orphan Drug Policies? *Value in Health* 2012; 15: 1185-91.

20 Divino V, DeKoven M, Kleinrock M, et al. Orphan Drug Expenditures In The United States: A Historical And Prospective Analysis, 2007-18. *Health Affairs* 2016; 35(9): 1588-1594.

21 Radley DC, Finkelstein SN, and Stafford RS. Off-Label Prescribing Among Office-Based Physicians. *Archives of Internal Medicine* 2006; 166: 1021-1026.

22 Zarkali A, Karegeorgopoulos DE, Rafailidis PI, et al. Frequency of the Off-

Appendix

- Label Use of Monoclonal Antibodies in Clinical Practice: A Systematic Review of the Literature. *Current Medical Research & Opinion* 2014; 30(3): 471-480.
- 23 Kesselheim AS, Myers JA, Solomon DH, et al. The Prevalence and Cost of Unapproved Uses of Top-Selling Orphan Drugs. *PLoS ONE* 2012; 7(2): e31894. doi: 10.1371/journal.pone.0031894.
- 24 Consumer Reports. Shopper's Guide to Prescription Drugs, Number 6: "Off-Label" Drug Use. *Consumer Reports Best Buy Drugs*, 2007. www.CRBestBuyDrugs.org
- 25 Ruelaz Maher A, Maglione M, Bagley S, et al. Efficacy and Comparative Effectiveness of Atypical Antipsychotic Medications for Off-Label Uses in Adults: A Systematic Review and Meta-Analysis. *JAMA* 2011; 306(12): 1359-1369.
- 26 Shamiliyan TA, Choi JY, Ramakrishnan R, et al. Preventive Pharmacologic Treatments for Episodic Migraine in Adults. *Journal of General Internal Medicine* 2013; 28(9): 1225-1237.
- 27 The 45 drugs were chosen based on an initial exploratory study of orphan drugs during the 2012-2014 timeframe using one randomly selected NDC per drug.
- 28 Teagarden JR, Unger TF, and Hirsch G. Access and Availability of Orphan Drugs in the United States: Advances or Cruel Hoaxes? *Expert Opinion on Orphan Drugs* 2014; 2(11): 1147-1150.
- 29 Cohen JP and Felix A. Are Payers Treating Orphan Drugs Differently? *Journal of Market Access & Health Policy*, 2014; 2: e23513.
- 30 Divino V, Dekoven M, Wang W, et al. The Budget Impact of Orphan Drugs in the U.S.: A 2007-2013 MIDAS Sales Data Analysis. *Blood* 2014; 124(21): 736-738.
- 31 Daniel MG, Pawlik TM, Fader AN, et al. The Orphan Drug Act: Restoring The Mission to Rare Diseases. *American Journal of Clinical Oncology* 2016; 39(2): 210-13.
- 32 U.S. Food and Drug Administration. Orphan Designation and Approvals. <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>
- 33 U.S. Food and Drug Administration. Highlights of Prescribing Information: KRYSTEXXA (09/2010). http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125293s00001bl.pdf
- 34 U.S. Food and Drug Administration. Drug@FDA: FDA Approved Drug Products. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>
- 35 <http://icd9cm.chrisendres.com/index.php>