The Rise of Orphan Drugs

While drugs are being introduced at higher price points – orphan drugs are being introduced at price points that are many times that of other types of drugs. From 1998 to 2017, the average annual cost for orphan drugs increased 26-fold, while the cost for specialty and traditional drugs doubled.

4x

They are being approved – and entering the market – at higher rates than ever before. Among newly launched drugs, **the share of orphan drugs increased more than 4-fold,** from 10% to 44%, over the same 20-year period.

They are also being prescribed in increasing numbers – often, for conditions that aren't orphan conditions and can be treated with other therapies. **In 2017, seven of the top 10 best-selling drugs were orphan drugs** that were widely prescribed for non-orphan indications and off-label uses.

As a result, **orphan drugs are one of the biggest factors driving out of control drug prices,** which puts coverage and care out of reach for millions of hardworking American families.

Introduction

Despite many efforts to contain health care costs, prescription drug expenditures continue to grow. According to the Centers for Medicare and Medicaid Services (CMS) estimates, the total national prescription drug spending has reached $333.4 billion in 2017.[1] In the 5 years between 2013 and 2017, the national drug spending increased 25.7%. A recent IQVIA report attributed the rapid growth in drug spending to the introduction of expensive specialty drugs used to treat complex, chronic, or rare conditions such as cancer, HIV, or Hepatitis C.[2] As a result, prescription drug spending is projected to increase to $435 billion by 2023.

Continuous and persistent annual price increases continue to receive a great deal of attention from both the general public and legislators. For example, federal and state lawmakers have introduced bills that would require greater transparency from drug makers on their price-setting practices. As of May 2019, 10 states have adopted laws governing prescription drug price transparency.

Most efforts to contain skyrocketing drug costs focus on price increases for drugs already on the market. The laws are triggered only when a price significantly increases beyond the current price. What has received less attention is the fact that drugs are increasingly launched at higher prices.

Drug makers are using the launch of their products as another venue for raising revenue. When drugs are launched at higher prices, even modest price increases, in percentage terms, can translate into additional large amounts that consumers, employers, governments, and health insurance providers must pay. Thus, by setting high launch prices, drug makers may even avoid triggering additional reporting requirements down the road.

The purpose of this study is to examine the trend in increasing launch prices for drugs approved by the Food and Drug Administration (FDA) over a 20-year period between 1998 and 2017. The study highlights the need for policy solutions to address the skyrocketing launch prices of drugs in addition to measures containing their annual prices increases.

Orphan Drug Act

The growth in orphan drug development followed the passage of the Orphan Drug Act (ODA) in 1983.[3] The ODA and its subsequent amendments provided numerous incentives for drug makers to develop therapies for rare diseases that otherwise might not be commercially viable due to small patient populations.[4] Among other benefits, the orphan designation qualifies the drug maker for the following:

1. Seven-year market exclusivity from the date of orphan designation approval;
2. A 50% tax credit for expenses incurred during clinical testing;
3. A waiver of New Drug Application fee.

To be eligible for incentives under the ODA, drug makers must obtain orphan designation from the FDA based on the rarity of the targeted disease. Orphan diseases are defined as those occurring in fewer than 200,000 people in the United States each year.

The ODA has been successful. The number of orphan drugs approved by the FDA exploded since the act's passage.[5] Many more are in development. However, some drug makers have exploited the ODA to gain premium pricing for drugs that are widely used in non-orphan indication. This led to the creation of blockbuster orphan drugs – drugs with approved orphan designation that achieve billions of dollars in sales.

Methods Summary

The study includes a list of novel therapeutic drugs approved by the FDA in 1998 – 2017. For each drug, we calculated the annual per-patient expenditure at its launch price, adjusted for inflation to 2017 prices. In addition, we categorized drugs by drug type (orphan, specialty, traditional) and therapeutic class.

In order to analyze our final dataset, summary statistics were generated for all continuous and categorical variables. For continuous variables, mean values were generated. For categorical variables, proportions were generated. For a more detailed methodology, please consult the Appendix.

Key Findings

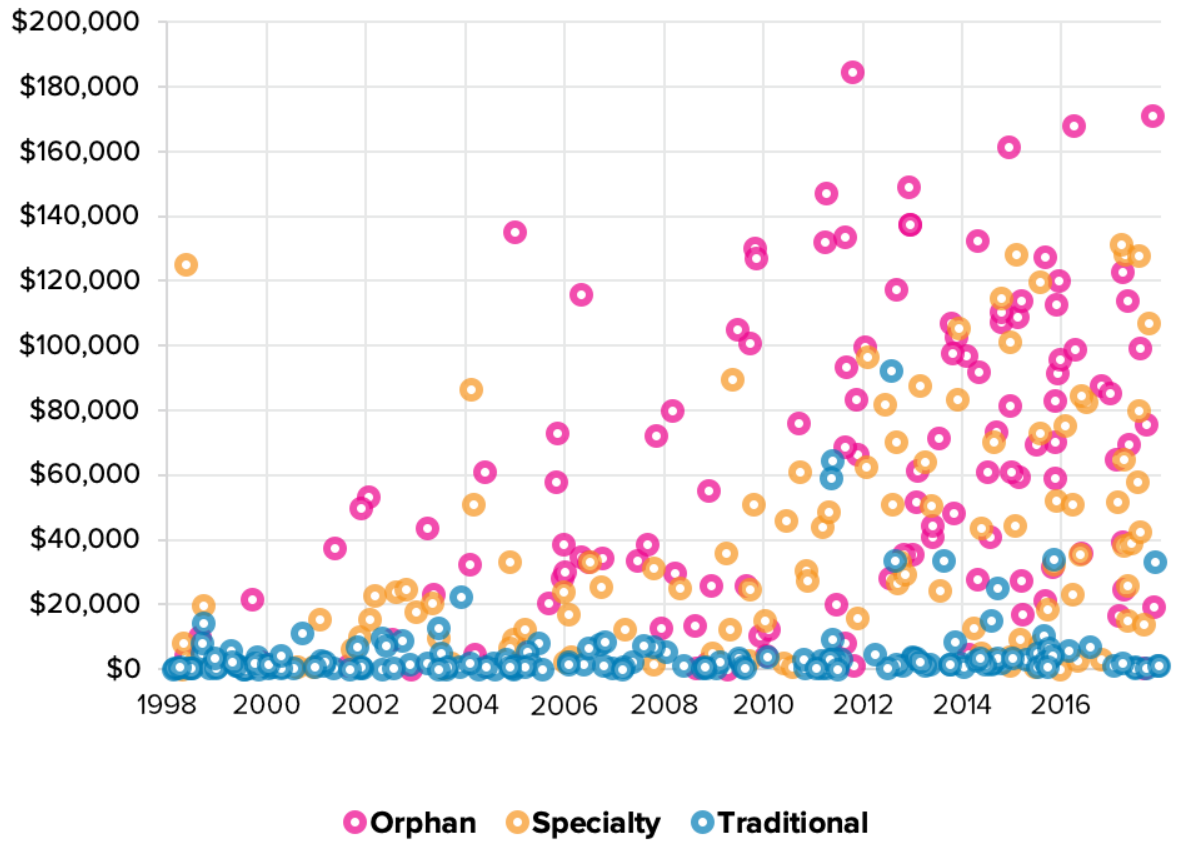
Our final sample contained 417 drugs approved in the two decades between 1998 and 2017 (Table 1). Of these, traditional brand drugs (traditional drugs) constituted the largest group (38%), followed closely by orphan drugs (35%). Specialty brand drugs (specialty drugs) accounted for slightly over a quarter of new drug approvals (26%).

Table 1. Average Annual Drug Cost by Type

Drugs	Average Annual Cost	Number of Drugs
All Drugs	**$55,560**	**417**
Traditional Drugs	$4,961	160 (38%)
Specialty Drugs	$38,309	110 (26%)
Orphan Drugs	$123,543	147 (35%)

The average annual per-patient expenditure at the launch price for all drugs in our sample was $55,560. The overall average masked a considerable variation in average annual drug cost by drug type. The average annual drug cost for traditional drugs was $4,961. In contrast, the average annual drug cost for orphan drugs was $123,543. Thus, orphan drugs were, on average, 25 times more expensive than traditional drugs. Specialty drugs fell in between, averaging $38,309 in annual costs. The difference in the average cost between orphan, specialty, and traditional drugs was statistically significant ($F_{2,414}$=200.73, p<0.001).

Figure 1. Annual Cost of Drugs at Launch: 1998-2017



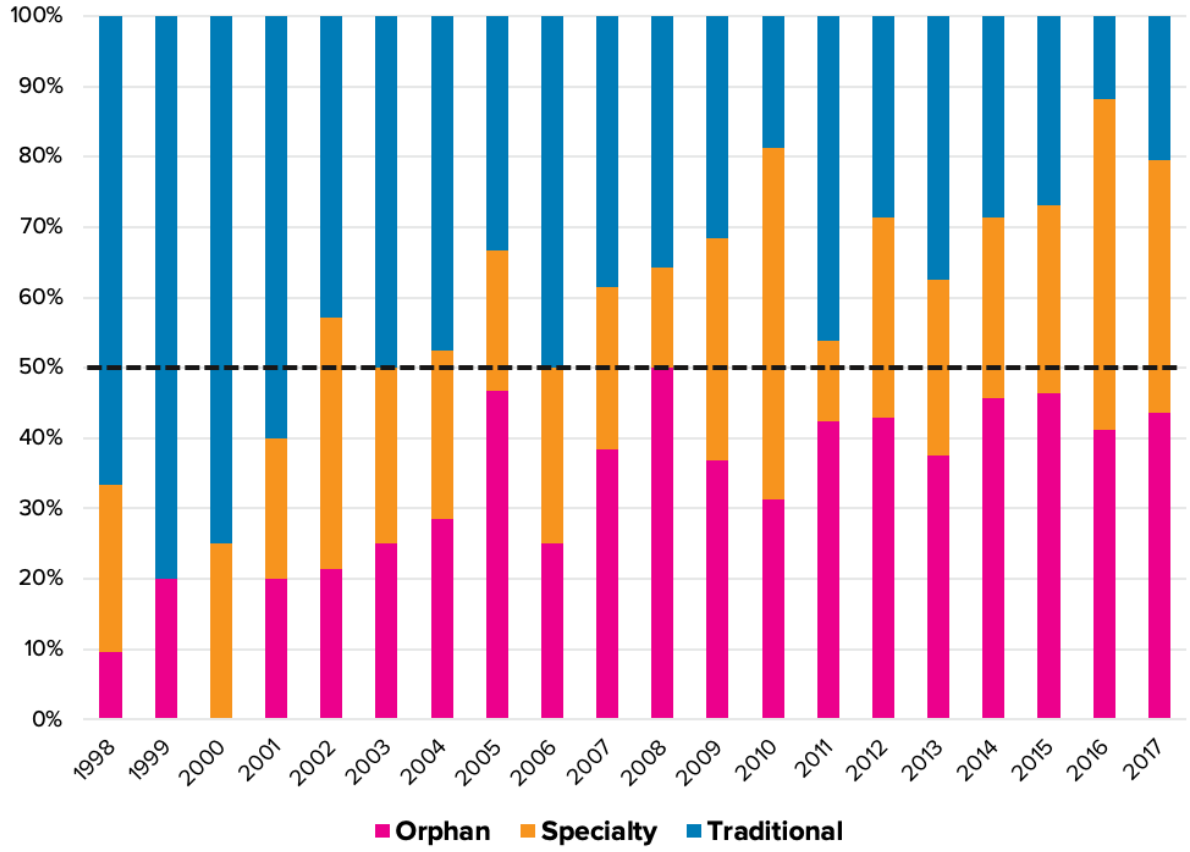
Note: 22 orphan drugs had an annual cost exceeding $200,000 and are not shown on this graph. See Appendix for a full sample graph.

Annual drug costs at launch have seen a substantial and sustained increase over the last 20 years (Figure 1). The average annual drug cost rose more than 10-fold from $9,781 in 1998 to $106,149 in 2017 (Table 3). Orphan drugs were a key driver behind the dramatic increase.

Growing Share of Orphan Drugs

The orphan drug share of new drug approvals has increased dramatically over the last 20 years (Figure 2). Starting from 10% of all drug approvals in 1998, it rose to 44% in 2017 – a more than 4-fold increase. As approvals of orphan drugs went up, approvals of traditional drugs went down. The share of traditional drug approvals declined from 65% in 1998 to only 20% in 2017. Since 2002, traditional drug approvals accounted for less than half of new drug approvals each year. The share of specialty drugs remained steady over the last 20 years.

Figure 2. Share of Drugs Approved in 1998-2017 by Type



Another way to illustrate the dramatic increase in the share of orphan drug approvals is to compare the first and second decades in our sample, which is subject to less year-on-year volatility in drug approvals. In the first decade (1998-2007), orphan drugs accounted for 23% of new drug approvals (Table 2). In the second decade (2008-2017), the orphan drug share increased to 42%. The difference between the proportions of orphan drugs in the first and second decades was statistically significant ($Z=3.95$, $p<0.001$).

Table 2. Orphan Drugs by Decade

	1998-2007	2008-2017
Orphan Drug Share	23%	42%
Average Annual Drug Cost	$77,828	$138,919

Drug makers' shift towards the more expensive orphan drugs can explain some of the increase in the average annual drug costs. Since orphan drugs were considerably more expensive than traditional drugs, the increasing share of orphan drugs has naturally led to the increasing average annual cost over the last 20 years. The share of specialty drugs remained stable through the 20-year period – neither increasing nor decreasing in a way that would unduly account for increasing drug prices.

Increasing Orphan Drugs Prices

Orphan drugs made prescription drugs more expensive, on average, as orphan drugs were launched at an increasing rate and with increasingly higher prices. In our sample, though the average annual drug cost has increased across all drug types, orphan drugs experienced the highest increase. The average annual drug cost for both traditional and specialty drugs has roughly doubled in the 20-year period. In contrast, the average annual cost for orphan drugs has skyrocketed from $7,136 in 1997 to $186,758 in 2017 – a 26-fold increase (Table 3).

Table 3. Average Annual Drug Cost by Year and Type

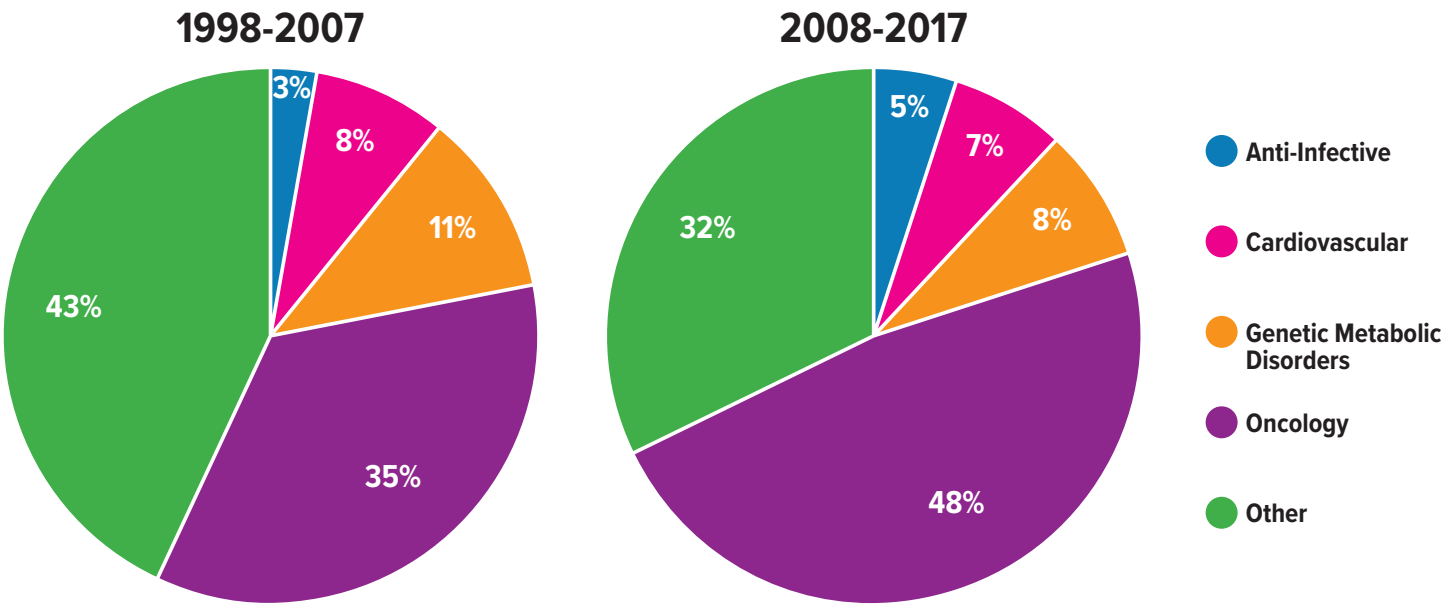
Year	All	Traditional Drugs	Specialty Drugs	Orphan Drugs
1998	$9,781	$2,542	$31,106	$7,136
1999	$2,982	$1,596	-	$8,526
2000	$2,037	$2,342	$1,122	-
2001	$9,045	$1,697	$10,621	$29,512
2002	$13,994	$4,692	$20,989	$20,941
2003	$43,756	$5,497	$8,146	$155,884
2004	$20,911	$1,098	$37,317	$40,263
2005	$63,625	$3,178	$12,998	$128,499
2006	$20,532	$3,782	$20,016	$54,547
2007	$59,063	$3,438	$15,003	$141,125
2008	$17,499	$1,617	$15,214	$29,497
2009	$38,271	$1,644	$36,184	$71,453
2010	$92,732	$2,478	$23,059	$258,360
2011	$46,020	$12,317	$36,256	$85,451
2012	$98,013	$17,643	$56,418	$179,322
2013	$45,766	$6,211	$69,380	$69,577
2014	$76,182	$5,852	$39,574	$140,731
2015	$65,855	$6,774	$44,292	$112,543
2016	$139,473	$6,367	$44,819	$285,680
2017	$106,149	$5,024	$66,053	$186,758

Comparing the two decades, the data shows that average annual cost for orphan drugs almost doubled from $77,828 in 1998-2007 to $138,919 in 2008-2017. This indicates a steady, long-term upward trend in orphan drug prices. The difference in average annual drug cost of orphan drugs in the first and second decades was statistically significant ($F_{1,145}$=11.83, $p<0.001$).

Orphan Drugs by Therapeutic Class

Orphan drugs in our sample were used to treat a wide variety of diseases, including genetically inherited metabolic disorders, cardiovascular diseases, pulmonary diseases, or multiple sclerosis. However, targeted cancer treatments constituted the single largest category of orphan drugs, with their share of new orphan drug approvals increasing over time. As shown in Figure 3, cancer drugs accounted for a third (35%) of all new orphan drug approvals in 1998-2007; they accounted for almost half (48%) of new orphan approvals in 2008-2017. The growing number of approved cancer treatments was responsible for a part of the overall growth of orphan drugs. However, even if we exclude orphan cancer treatments from the sample, the share of orphan drugs would still be 16% in 1998-2007 and 27% in 2008-2017, compared to 23% and 42% respectively.

Figure 3. Orphan Drugs by Therapeutic Class



Economic Impact of Orphan Drugs

While many of the diseases targeted by orphan drugs are rare conditions that affect very limited populations, some orphan drugs are used to treat diseases that are not rare conditions. In fact, there are several examples of orphan drugs being used to treat autoimmune diseases. Remicade, the first anti-TNF agent on the market, was originally approved for the treatment of Crohn's disease, a rare condition that allowed Remicade to receive orphan designation.[6] A year later, it was approved for the treatment of rheumatoid arthritis, a common disease affecting over a million Americans.[7] Over time, Remicade was approved for treatment of other common diseases, such as psoriatic arthritis and ulcerative colitis.

Conversely, Enbrel, the second anti-TNF agent to come to the market, was originally approved for the treatment of rheumatoid arthritis but was approved for an orphan indication a year later. Humira, another popular anti-TNF agent, followed the same strategy. As a result, in 2017, Humira topped the ranking of best-selling drugs with $18.4 billion in worldwide sales (Table 4).[8] Remicade and Enbrel also made the list of top 10 best-selling drugs with $5.8 billion and $5.4 billion in sales, respectively.

Table 4. Blockbuster Orphan Drugs

Drug	Initial Market Approval	Orphan Indication Approval	Global Sales in 2017 ($ billions)	Global Sales Rank in 2017
Anti-TNF agents				
Humira	2002	2008	$18.4	1
Remicade	1998	1998	$5.8	6
Enbrel	1998	1999	$5.4	8
Oncology				
Revlimid	2005	2005	$8.2	2
Rituxan	1997	1997	$7.5	3
Herceptin	1998	2010	$7.1	4
Avastin	2004	2009	$6.8	5

Table 4. Blockbuster Orphan Drugs (continued)

Drug	Initial Market Approval	Orphan Indication Approval	Global Sales in 2018 ($ billions)	Global Sales Rank in 2018
Anti-TNF agents				
Humira	2002	2008	$19.9	1
Oncology				
Revlimid	2005	2005	$9.7	2
Keytruda	2014	2014	$7.3	3
Herceptin	1998	2010	$7.1	4
Avastin	2004	2009	$7.0	5
Rituxan	1997	1997	$6.9	6
Opdivo	2014	2014	$6.7	7

Similarly, all 4 cancer drugs on the top 10 best-selling drugs list in 2017 have been approved for orphan indications. Both Revlimid and Rituxan, the second and third best-selling drug with $8.2 billion and $7.5 billion in sales, were initially approved as orphan drugs. In contrast, Herceptin and Avastin, fourth and fifth top selling drugs, were approved for an orphan indication several years after the initial market approval. Two newer cancer drugs, Keytruda and Opdivo, broke into the top 10 list in 2018 with $7.2 billion and $6.7 billion in sales, respectively.[9] Both were approved in 2014 as orphan drugs.

The multibillion-dollar revenues generated by the orphan drugs come primarily from their non-orphan and off-label use. A recent AHIP study examined utilization of orphan drugs by on-label orphan, on-label non-orphan, and off-label use for a sample of 45 orphan drugs.[10] The study found that the cancer drug Rituxan was used for an orphan indication in only 12.5% of cases. Avastin was used for orphan indications in 7.8% of cases, while Herceptin's share of orphan use was 2.2%. For autoimmune disease drugs, the share of orphan use was 4.5% for Remicade and 1.9% for Humira. Even though orphan uses constitute a small share of drug utilization, these orphan drugs benefit from the various incentives provided under the ODA, including certain tax breaks and 7-year exclusivity for orphan indication.

Conclusion

Drug launch prices have increased substantially over the past 20 years. The average annual drug cost has seen a 10-fold increase from 1998 to 2017. Much of this increase was driven by orphan drugs. First, the orphan drugs' share of all new drug approvals has increased more than 4-fold over the study period. The increased share came at the expense of cheaper traditional drugs. The share of specialty drugs was steady through the study period. Second, orphan drugs became more expensive over time. Average annual drug costs have increased across all drug types, but orphan drugs experienced the greatest increase. While average drug costs for traditional and specialty drugs have doubled in the 20-year period, average orphan drug cost saw a 26-fold increase.

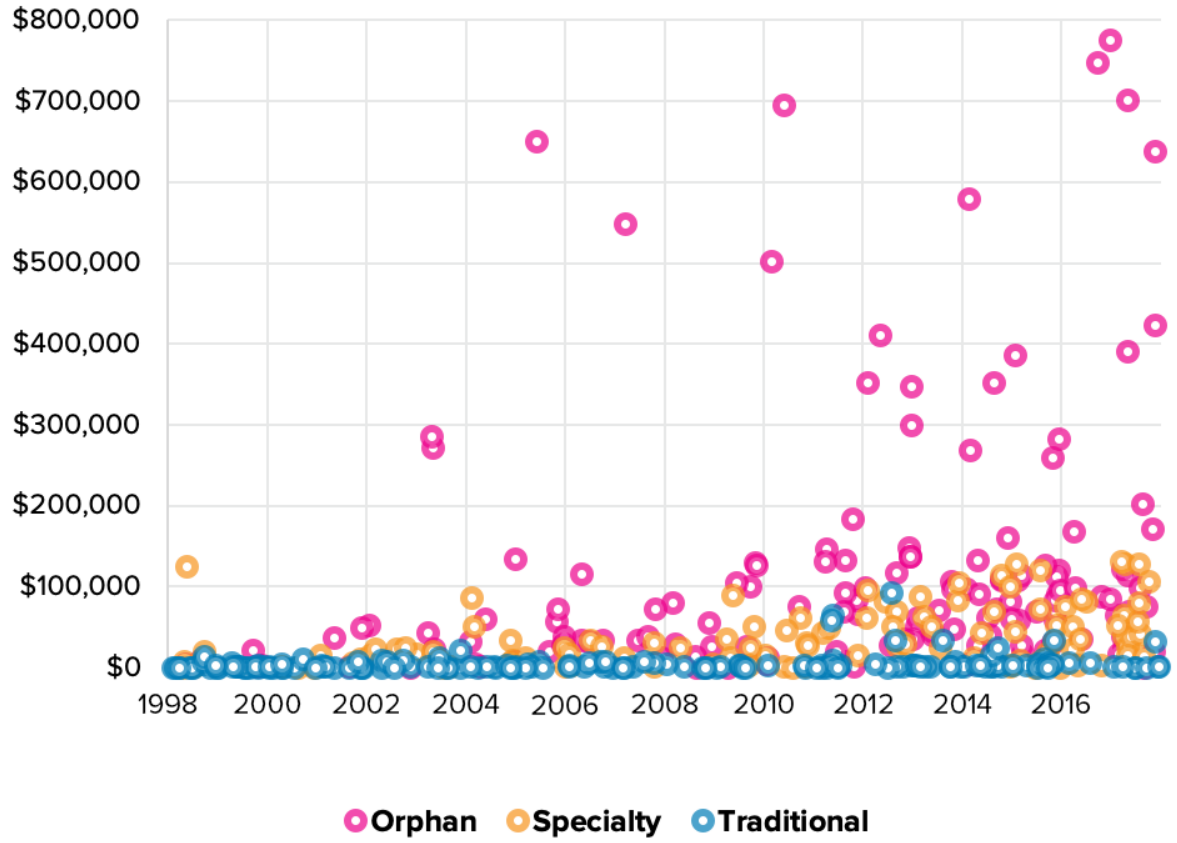
The pharmaceutical industry points to small patient populations in order to justify exceptionally high prices on orphan drugs. Yet, the argument fails to explain the extraordinary year-over-year launch price increases for orphan drugs. Further, since orphan drugs throughout the study period address many of the same diseases, small target population cannot explain the continuous increases in orphan drug launch prices.

It may be tempting to dismiss the growth in the share and launch prices of orphan drugs as having only a limited impact on the overall health care costs. However, the target patient population for orphan drugs may not be as small as portrayed by the pharmaceutical industry. Many orphan drugs have non-orphan indications in addition to their orphan indications. Furthermore, many orphan drugs are used off-label, suggesting a larger market for the drugs than their approved indications may show. Not surprisingly, the list of top 10 best-selling drugs in 2017 included 7 drugs with orphan indications. As a result, we are treating common diseases at orphan-high prices.

The skyrocketing drug prices add to the urgency for lawmakers to revisit and revise the Orphan Drug Act. Lawmakers must ensure that the Act serves its original purpose to incentivize the development of treatments for rare diseases – not as a gateway to premium pricing and blockbuster sales beyond orphan indications.

Appendix

Annual Cost of Drugs at Launch: 1998-2017 (full sample)



Detailed Methodology

Inclusion/Exclusion Criteria

For this study, we compiled a list of all novel prescription drugs approved by the FDA in the 1998 – 2017 time period. The list of approved prescription drugs was compiled using the FDA's online Drugs@FDA tool.[11] The online search tool allows searching for new drug approvals, including new molecular entities and biologics, by months. To compile the initial list of all applications approved for the first time in 1998 – 2017, the list of drugs approved in each month of the 20-year period was obtained and compiled into the overall list.

The study used the following inclusion/exclusion criteria to compile the final drug list.

- Drugs that were not therapeutic in nature, e.g., agents used in imaging or diagnostics, general anesthesia drugs, and contraceptives, were excluded. The study focused only on drugs that were used to treat diseases.
- Ophthalmic and topical drugs were excluded due to difficulties in estimating annual dosage requirements.
- Drugs were excluded from the list if the FDA website did not contain the original drug label issued at the time of drug launch. Estimates of annual drug cost at launch were based in large part on the dosing information obtained from the FDA label. Since FDA labels issued at a later date might change recommended doses or contain new indications, they could not be used as a substitute for the original label.
- Drugs were included in the list only if the earliest recorded price in the REDBOOK dataset was within 180 days of the drug approval date. The launch price was considered unavailable for drugs with the earliest price recorded more than 180 days after the drug approval. These drugs were excluded from the study.

Variable Descriptions

Annual Drug Cost

The annual cost of prescription drugs at launch was calculated as the launch price multiplied by the total annual utilization of the drug.

Launch Price

For each drug, the earliest available Average Wholesale Price (AWP) unit price listed in the March 2018 edition of the REDBOOK was recorded. If the earliest recorded price was established within 180 days after the drug approval date, then the price was assumed to be the launch price of the drug. If the earliest recorded price was later than 180 days after the drug approval date, then the drug was excluded from the sample.

The AWP unit price was further divided by the strength of the drug formulation in order to obtain per mg or per mcg AWP price. For drugs with different strength and package size options, the average per mg AWP price was calculated. As a final step, all prices were adjusted for inflation to 2017 prices using the prescription drugs component of the Consumer Price Index published by the Bureau of Labor Statistics.[12]

Annual Utilization

For each drug, estimates of the annual utilization, for a typical patient, were calculated based upon the standard dosing information found in the initial FDA-approved labeling. The daily dose of the drug, typically expressed by weight (mg or mcg), was estimated. The frequency of dosing and the duration of treatment were used to estimate the total number of daily doses of a drug administered during the year. The total number of daily doses was then multiplied by the daily dose of a drug to estimate the total annual utilization of the drug, expressed by weight.

We took the following into consideration:

1. Standard dosing assumptions:
    a. When a recommended dose was specified as a range, an average dose was assumed.
    b. Unless otherwise specified, all patients were assumed to be non-elderly adults.
    c. Commonly accepted estimates of age-appropriate male body weight or body surface area were used for those medications dosed by body weight or body surface area.[13] Adult body weight was assumed to equal 75kg. Adult body surface area was assumed to equal 1.8m^2.
    d. For pediatric drugs, the standard dosing was calculated for 9-year-old boys. Body weight was obtained from the CDC Clinical Growth Charts at 50th percentile weight for a 9-year-old boy.[14] It was assumed to equal 29kg. Body surface area was calculated using Mosteller's formula based on weight and height of a 9-year-old boy.[15] It was assumed to equal 1.0m^2.
    e. For drugs targeting Duchene muscular dystrophy, Emflanza and Exondys 51, the standard dosing was calculated for 10-year-old boys, which was the mean age of patients tested in clinical trials for these drugs. Based on CDC Clinical Growth Charts, body weight was assumed to equal 32kg.
    f. For drugs targeting IGF-1 deficiency, Increlix and Iplex, the standard dosing was calculated for 6-year-old boys, which was a conservative measure. The median age of patients tested in clinical trials was 6.7 and 8.7 years; the median bone age was 4.2 and 5.9 years. Based on CDC Clinical Growth Charts, body weight was assumed to equal 21kg.

2. Duration of treatment assumptions:
    a. For those drugs that had duration of treatment indicated in the label in the Dosage and Administration section, the given duration was used in the study. If the duration was given as a range or if several durations of treatment were given for different indications, the longest duration of treatment was used in the study.
    b. When the duration of treatment was not indicated in the Dosage and Administration section, it was obtained from the Clinical Trials section.
        i. For oncology drugs, the duration of treatment was assumed to equal the median duration of exposure to the drug during the clinical trial. The assumption was necessary to account for patients discontinuing treatment due to nonresponse and tolerance issues. If more than one clinical trial were reported on the label, the longest median duration of exposure was used.
        ii. For all other drugs, the duration of treatment was assumed to equal the length of the clinical trial. If more than one clinical trial were reported on the label, the longest clinical trial duration was used.
    c. For several drugs, the Clinical Trials section did not indicate duration. In these cases, a clinical trial study for the given drug published in an academic journal close to the time of drug approval was used to obtain the duration of treatment.
    d. In all cases, the duration of treatment was assumed to equal 12 months if the indicated duration of treatment exceeded 12 months.
    e. All treatment duration times were standardized. A year was counted as 365 days, 52 weeks or 12 months depending on dosing frequency. Half a year was counted as 180 days, 26 weeks or 6 months. A quarter was counted as 90 days, 12 weeks or 3 months. Clinical trials that lasted 48 weeks were counted as lasting a year. Clinical trials that lasted at least 24 weeks were counted as lasting half a year.

Drug Approval Date

The initial approval date was obtained from the FDA's online Drugs@FDA tool.

Drug Approval Decade

Drugs were categorized into the following two groups based on the initial approval date:

1. *First Decade:* drugs approved between January 1, 1998 and December 31, 2007
2. *Second Decade:* drugs approved between January 1, 2008 and December 31, 2017

Drug Type

Drugs were classified by type into the following three mutually exclusive categories:

1. Orphan Drugs
2. Specialty Drugs
3. Traditional Drugs

Orphan drug status was identified using the FDA's online Orphan Product Designation Search Page.[16] Only drugs that received FDA's orphan designation for the initial approved indication were counted as orphan drugs. Prescription drugs that received orphan designation for a new indication after their initial market approval were not counted as orphan drugs.

Specialty drug status was obtained from publicly available specialty drug formularies from the following major health insurers: Aetna[17], Cigna[18], and Blue Shield of California[19]. A drug was counted as a specialty drug if it was listed in at least two of the three specialty formularies. In addition, drugs that were administered though intravenous (IV) infusion were counted as specialty drugs as they would normally be administered in a physician's office or a hospital. Drugs with multiple routes of administrations were not counted as IV drugs. Only non-orphan drugs were included in the specialty category; orphan drugs that appeared in specialty drug formularies were counted as orphan drugs.

Traditional Drugs category included all the remaining drugs that did not fall into either orphan or specialty categories.

Therapeutic Class

For each drug, Therapeutic Class Code listed in the March 2018 edition of the REDBOOK was recorded. The REDBOOK Therapeutic Class Code uses the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification, which groups of drugs with similar pharmacologic, therapeutic, and/or chemical characteristics in a 4-tier hierarchy. The first, highest tier lists the therapeutic class of the drug. Based on the therapeutic class, drugs were classified into the following categories:

1. Anti-Infective (therapeutic class – 08)
2. Cardiovascular (therapeutic class – 24)
3. Genetic Metabolic Disorders (therapeutic class – 44)
4. Oncology (therapeutic class – 10)
5. Other

Analytical Approach

In order to analyze our final dataset, summary statistics were generated for all continuous and categorical variables. For continuous variables, mean values were generated. For categorical variables, proportions were generated.

Two statistical comparisons were conducted on the full dataset. A one-way analysis of variance (ANOVA) was conducted to compare the main effects of Drug Type on the Annual Drug Cost. Drug Type included three levels (Orphan, Specialty, Traditional). The natural logarithm of the Annual Drug Cost was used in ANOVA test in order to correct for skewness in data. A two sample Z-test for proportions was conducted to compare the proportion of orphan drugs in the First and Second Drug Approval Decades.

Another statistical comparison was run on a subset that included orphan drugs only. An ANOVA test was conducted to compare the main effects of Drug Approval Decade on the natural logarithm of the Annual Drug Cost. Drug Approval Decade included two levels (First Decade, Second Decade). The *a priori* assumption for all tests of significance was set at *alpha=0.05*.

Endnotes

1 Martin, Anne B., Micah Hartman, Benjamin Washington, Aaron Catlin, and National Health Expenditure Accounts Team. "National Health Care Spending in 2017: Growth Slows to Post–Great Recession Rates; Share of GDP Stabilizes." *Health Affairs* (2018): 10-1377.

2 IQVIA. "Medicine Use and Spending in the U.S.: A Review of 2018 and Outlook to 2023," May 2019

3 Loughnot, David. "Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?" *American Journal of Law & Medicine* 31, no. 2-3 (2005): 365-380.

4 Food and Drug Administration. The Orphan Drug Act, Relevant Excerpts. Available at https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts

5 Haffner, M. History of Orphan Drug Regulation—United States and Beyond. *Clinical Pharmacology & Therapeutics* 100 (2016): 342-343.

6 Food and Drug Administration. Orphan Product Designation Search. Available at https://www.accessdata.fda.gov/scripts/opdlisting/oopd

7 Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. Available at https://www.accessdata.fda.gov

8 Urquhart, Lisa. "Market watch: top drugs and companies by sales in 2017." *Nature Reviews Drug Discovery* 17 (2018): 232.

9 Urquhart, Lisa. "Market watch: top drugs and companies by sales in 2017." *Nature Reviews Drug Discovery* 18 (2019): 245.

10 AHIP Data Brief. 2016. "Orphan Drug Utilization and Pricing Patterns (2012 - 2014)." Available at https://www.ahip.org/orphan-drug-utilization-and-pricing-patterns-2012-2014/

11 Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. Available at https://www.accessdata.fda.gov

12 Bureau of Labor Statistics. Consumer Price Index. Available at https://www.bls.gov/cpi/data.htm

13 Verbraecken, Johan, Paul Van de Heyning, Wilfried De Backer, and Luc Van Gaal. "Body Surface Area in Normal-Weight, Overweight, and Obese Adults. A Comparison Study." *Metabolism* 55, no. 4 (2006): 515-524.

14 Centers for Disease Control and Prevention, National Center for Health Statistics. Clinical Growth Charts. Available at https://www.cdc.gov/growthcharts/clinical_charts.htm

15 Mosteller, R. D. "Simplified Calculation of Body Surface Area." *New England Journal of Medicine* 317 (1987): 1098.

16 Food and Drug Administration. Orphan Product Designation Search. Available at https://www.accessdata.fda.gov/scripts/opdlisting/oopd

17 Aetna. Specialty Drug coverage reviews. https://pbm.aetna.com/portal/asset/aetna_specialty_guideline_management_drug_list.pdf

18 Cigna. Specialty Pharmacy List. https://www.cignaclientresources.com/crp/GetFile.ashx?fileId=343

19 Blue Shield of California. Specialty Drug List for Standard Drug Formulary. https://www.blueshieldca.com/bsca/documents/pharmacy/Specialty_Drugs_List_Standard_Formulary.pdf