Generic Entry and The Effect on Prices in the Prescription Drug Market

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Abstract

Drug firms have utilized a variety of strategies that contribute to rising drug prices in the U.S. for the last few years. Strategic entry timing and number of indications a drug is approved might be two factors that contribute to this rise in prices. While there have been some studies uncovering a positive relationship between generic entry and branded prices, there has been little research done on the effects of generic entry on generic prices thus far. This work can impact policy aimed at decreasing generic drug prices and increasing competition in the generic drug market.

Oncology and inflammatory bowel disease (IBD) are two disease areas that have a high price burden to patients in the U.S. today, hence using Medicare Part B Average Sales Price (ASP) data, I analyze the effect of entry timing on the price of 24 drugs in these two indication areas. Using the Drugs@FDA Database, I collect data on the FDA approval date of a drug, and on the indications a drug is approved for. Utilizing OLS, my results suggest that later entry times lead to lower drug prices, with a 1 year increase in entry time resulting in a 6.99% increase in prices. Results also suggest that an increase of 1 in the number of indications a drug is approved for leads to a 49.79% decrease in drug price. This could suggest that having existing generic competitors in the pharmaceutical market decreases generic prices, and that number of indications is a strong indicator of drug price.

If the current work is confirmed by future studies similar to this studying entry time and price in the generic pharmaceutical market, it is possible that future drug policy should focus on promoting competition within the pharmaceutical market to lower generic prices.

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Amidst rising drug prices and overall healthcare expenditure in the United States, many are wondering how patients can keep up with the rising out-of-pocket healthcare prices. A few select groups in particular--cancer, and inflammatory bowel disease (IBD) patients--have felt the burden of these rising prices, and make up a large, growing, sector of the U.S. population. There are currently 1.7 million cancer patients, and 3 million people with IBD (CDC, 2021). It is projected that the cancer incidence rate will increase 49% from 2015 onwards (Weir et al., 2021), and IBD rates will increase by 17% (Alatab et al., 2020). Since 2012, chemotherapy injection prices have increased by more than 25% (Leighl et al., 2021), and IBD drug prices have increased by more than 30% (Park et al., 2019). These numbers are all much higher than the overall drug price increases in the same time frame (2018-2021), which have been estimated to be around 3% (Bunis, 2021). Given the large financial and health policy consequences of rising drug prices within these three indications, it is important to examine the market factors at play leading to rising prices.

Many factors, such as entry timing in the market, market share, number of direct competitors, average rebate discount, and patent litigation, have been shown to be correlated with drug price (Regan, 2008; Remuzat et al., 2017; Grabowski et al., 2007). With growing numbers of pharmaceutical companies investing in drug development (CBO, 2021), competition within and timing of entry in this market seem to be particularly salient variables to analyze in relation to drug pricing. Hence, the analysis of the relationship between drug launch time, also referred to as entry time, and generic drug average sales price is what will be focused on in this study. To that end, my research will analyze how entry timing in the drug markets for oncology and IBD drugs affects existing pricing of these drugs.

This could give us insight into strategies to promote or disincentivize generic competition in the industry, depending on the results. The health policy implications could also be far-reaching, in terms of FDA approval process timelines for new generic drugs, and clinical testing of efficacy and safety pipelines (Gupta et al., 2019). These timelines could be greatly affected by analyses of entry timing on price, especially since the price of competitors' drugs and launch time are closely related to the launch time and price of comparable drugs (Frank & Salkever, 2004).

The established regulatory landscape around generic drugs is important to discuss, as it has been the source of much debate in health policy reform discussions surrounding how to decrease consumer drug spending in the U.S. The Waxman-Hatch Act, under The Drug Price Competition and Patent Term Restoration Act of 1984, made changes to generic drug approval processes that "allows for approval of a generic copy of a previously approved "pioneer" drug product without the submission of a full new drug application" (Coster, 2007). Hence, there has been an explosive increase, since this act, in the amount of generic prescriptions in the U.S. (CBO, 2022). The same trend follows for branded drugs, as competition within branded drugs has increased (Sarpatwari et al., 2019).

However, the process is still comprehensive, including an investigational drug review, with the average timeline for any new generic or branded drug to be approved at 12 years (FDA; Norman, 2016). While the median FDA review time has decreased slightly due to the aforementioned policies, the full time from beginning of clinical testing to approval has remained relatively stable (Advisory, 2020).

Despite this stagnation in drug approval timelines, many loopholes in the Waxman-Hatch Act, to maximize monopoly profits, have been used by the brand name drug industry, leading

many to call for policy reform against high prescription drug spending as a result (Meagher, 2017). The FDA also firmly establishes through studies over many years that generic competition is linked to lower generic drug prices (FDA, 2019). However, in recent years, generic competition has been undermined by strategies employed by brand-name manufacturers, causing generic drug versions to increase wildly in price (Schondelmeyer, 2022). Factors in addition to the number of competitors could be important in analyzing this generic drug price increase, in relation to competition in the industry.

An important definition to include is that of biosimilars, which is key in the regulatory landscape of drugs today. Biosimilar drugs are defined as the following by the FDA: "A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product." A reference product is one that is already approved by the FDA, based on comprehensive safety and effectiveness data (FDA, 2017), and a biological product is "a large, complex molecule…produced through biotechnology in a living system" (FDA, 2018). Hence, biosimilars are comparable, sometimes substitutable drugs, to already approved brand-name drugs on the market. Examples of biosimilars include Hulio, a similar drug to Humira, the popular blockbuster drug for arthritis, plaque psoriasis, and ulcerative colitis. Biosimilars and generics are versions of brand name drugs that can be more affordable treatments. Usually, reference products have what we call Loss of Exclusivity, or LoE, dates. These dates signify when the patent on the drug expires, and are issued by the government's collaboration with the pharmaceutical manufacturer. Oftentimes, biosimilars are more affordable than their counterpart reference drugs (Goldman & Phillipson, 2021), spurring the question of why more biosimilars are not approved yet in the U.S. today to alleviate rising drug prices. This often comes down to the complex relationship between entry time (FDA

approval) of a drug, pricing of the drug, and current, non-biosimilar substitutes for the drug on the market (Zhai et al., 2019).

Current research leaves much room to be explored on how exactly drug pricing correlates with 1. launch timing (FDA approval date) and 2. entry time of competitors following launch time. This area is relatively new and unexplored, though there have been a few papers regarding patent challenges and their effects on market exclusivity (Grabowski, 2017; Kesselheim et al., 2017; Kesselheim, 2007). However, these mainly focus on patent expiry date data, rather than pricing data. Hence, the focus of this paper will be to elucidate the relationship between entry and pricing of generic drugs in two pertinent markets, IBD and oncology drugs. First, relevant literature will be discussed further, and then, a relevant economic framework for analyzing this question using regression models will be discussed in section III. Then, the pricing data used along with variables of particular interest will be focused on, and the results of the study will be presented. Lastly, the implications of this study for future pricing studies in the pharmaceutical landscape will be expanded upon in the conclusion.

Literature Review

Many studies help us to analyze the key motivation for choosing the specific indication areas of IBD and oncology for this current study, and give a comprehensive background of the drug landscape in these two indication classes. One such paper regarding oncology drugs that is important is Vandegrift and Datta's 2006 study. This paper succinctly examines the factors driving rising prescription drug costs in the U.S.-- such as an aging population, rising income, and new drug approvals-- and discusses how the aging U.S. population will contribute to new drug approvals for indications such as obesity and cancer. This study motivates the current study's focus on oncology and IBD products, both indications with a large patient burden.

Understanding the theoretical work done on generic and branded drug entry and price landscape is key, though few studies focus only on generic or branded drugs. With regards to generic entry and price competition in the pharmaceutical market, a 2008 study by Tracy Regan used an important theoretical framework called the Generic Competition Paradox. The most commonly accepted explanation to the hypothesis that branded firms raise their price in response to generic entry is currently the Generic Competition Paradox, hence this hypothesis was tested by Regan. Using this, Regan found that generic entry has a positive effect on branded prescription prices. The methods of analysis that contain an empirical model using log(price per prescription) as a dependent variable, can greatly help this study in its empirical framework grounding, and serve as a check of whether or not traditional economic theory of increased suppliers decreasing equilibrium price does not indeed hold up in pharmaceutical markets, as the study finds. The same Generic Competition Paradox used by Regan is independently tested in this study, as is the log(price per prescription) model specification. The main difference is that the Regan study focuses on generic entry and branded prices, whereas this study will focus on generic entry and generic prices.

A 2004 study by Frank & Salkever estimates models of price responses by brand-name and generic drugs to generic entry, and finds that brand-name prices increase after generic entry, followed by a decrease in the price of generic drugs, very similar to the Regan 2008 study aforementioned. While the regression methods differ in their study and the current study, two specific parts of the variable use and specification in Frank & Salkever's model prove to be useful. One, the use of market size as an instrumental variable is justified due to it not being related to price, but with a potential impact on making market entry more or less attractive (82). The use of market size as an IV is crucial to this study and will be adopted from Frank &

Salkever's study. Secondly, the use of a dummy variable in their study to account for drugs used for chronic conditions possibly having different pricing dynamics led them to fail to "reject the hypothesis that drugs used for different types of illnesses had different price responses to competition" (87). That conclusion reached by their paper directly motivates this study's empirical model specification, in controlling for the type of drug, indications a drug is approved for, and status of a drug.

A theoretical framework that is used in the Grabowski et al. 2007 study is a monopolistic competition model, to explain how biosimilar investment costs lead to fewer competitors and less price erosion than in markets facing generic competition. The results find a positive relationship between originator and biosimilar price difference and number of biosimilars entering the market; as the price difference increases, the number of biosimilars does as well. Specifically within Grabowski's study, the combination of a theoretical model of generic drugs with regression estimates from biosimilar pharmaceuticals to estimate market entry and prices, is of interest. One aspect of this theoretical approach will be adopted in the current study; specifically, regression estimates from generic pharmaceutical models are applied, with the relevant pricing data. This study also attempts to estimate market entry and prices in the generic biologic market by modeling generic pharmaceutical entry in itself as a function of market size. Their study could help this study in providing a roadmap for adding robust data to the market size variable, in terms of sales data. Additionally, the monopolistic competition model used in the Grabowski study will also be used in this study as a theoretical framework on which to study generic entrants and competition in the market.

Similarly, the market-wide effects of generic competition is particularly important, especially when studying generic entry in the generic market. Castanheira et al. (2019) posit that

the change between phase (1)--before generic entry, x number of firms having a monopoly on their molecule (likely a duopoly), and doctors have to choose between the 2-- and phase (2)--one of the molecules loses exclusivity, while the other remains, in what is called an asymmetric competition shock. They posit that this theoretical asymmetry arises from the fact that a generic is a perfect substitute for one molecule; one that is in an otherwise horizontally differentiated industry, where the distinctions between products are not easy to make based on quality. While not a 'shock' in terms of the typical economic market entry sense of the word, the authors mean this shock to focus on the fact that one company loses exclusivity over the product. The following can provide us with a theoretical framework within which to think about the study: "The rationale is that the more substitutable the two goods are, the more aggressively A and B compete prior to generic entry, in phase 1. This translates into initially lower prices and higher promotion. In that situation, generic entry has a comparatively small impact on prices: the reduction in promotion dominates. *High* levels of differentiation have the opposite effect: prices are initially high and promotion low. Then, generic entry primarily affects prices: both A's and B's prices drop" (Castanheira et al., 2019). These findings are in line with Regan's 2008 study and will be important to elucidate the effect of generic market drivers. The finding in Castanheira's study that high levels of differentiation due to generic entry leads to lower prices for all generic products can be tested through this study, and directly motivates the empirical model specification of looking at the effect of entry time on price. The idea of the asymmetric competition shock posed in the Castanheira paper directly drives the theoretical rationale for using variables such as patent expiry in this study.

A study by Olson and Wendling (2013) with the FTC Bureau of Economics identifies the effects of generic competitors on generic drug prices by using the 180-day marketing exclusivity

period created by the Hatch-Waxman Act. The drugs focused on are all oral solid medications, with no particular class/indication of drug excluded. They find that additional generic competitors lower generic drug prices greater during the 180-day exclusivity period than out of it, which could be important in foreshadowing an endogeneity bias in our model. They find that "endogenous entry introduces an attenuation bias in the estimates of the effects of the second and third competitors on price, which biases marginal effect estimates of later entrants" (Olson & Wendling, 2013), which is important to keep in mind to address in the model of this study. While fully eliminating it might not be possible, controlling as much as possible for attenuation bias of entrants outside a 180-day exclusivity period of a generic drug may be important.

While many of these studies focus on different aspects of the branded and generic drug price and entry landscape, no studies yet have exclusively focused on the effect of generic drug entry on generic drug price, especially focused within two drug classes (IBD, oncology). This study will build upon the initial asymmetric competition model framework posited by Castanheira et al. (2019), while changing certain model specifications used in the 1997 Frank & Salkever study, 2008 Regan study, and 2007 Grabowski model, which focus more on branded price and biosimilars, respectively. Other than these key studies, not many focus on generic or branded drug pricing, mainly due to the lack of drug pricing data, which in this study, will be circumvented by using Medicare Part B drug pricing data.

Theoretical Framework

The "Generic Competition Paradox", coined in 1993 by F.M. Scherer, is the hypothesis that the most common response--in a pharmaceutical market--to generic entry is for branded firms to raise their prices, and for generic incumbent firms to maintain or increase their prices, and cede significant market share to lower-priced competitors. One explanation for this

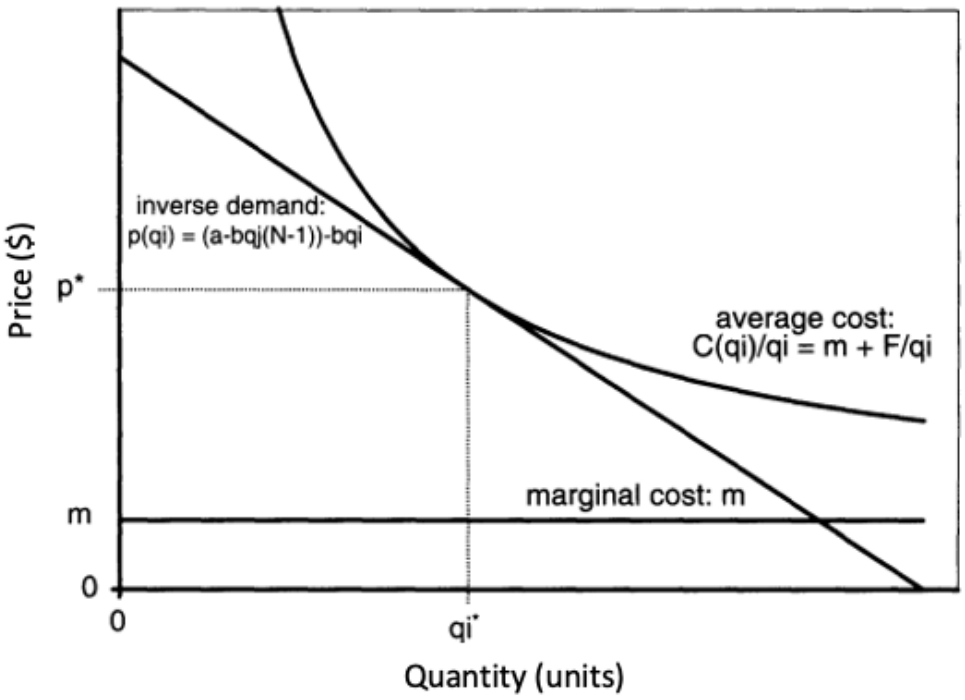
phenomenon relevant in our case, is that physicians tend to be risk-averse, and hence, prescribe brand name drugs out of habit as opposed to lower-price generic substitutes (Scherer, 1993). Patients could also prefer brand name drugs based on perception of higher quality. Using this framework as a basis, several studies have found either that 1) generic entry has a negative relationship with branded prices, thus disproving the hypothesis posed by Scherer (Caves et al., 1991; Wiggins and Maness, 2004), or that 2) generic entry has a positive relationship with branded drug prices (Frank & Salkever, 1997; Grabowski & Vernon, 1996), in line with the Generic Competition Paradox. However, these studies focused exclusively on drug patents that had expired, and the effect of this loss of exclusivity patent on branded drug prices. Since this theory does not offer a consistent and clear prediction across studies, this current study will prove to be an independent, novel test of how generic drug prices respond to generic entry. It will also add color to what other, if any, variables have an effect on this price increase/decrease, such as number and type of indications, number of competitors during time of launch, and presence of biosimilars.

The Theory of Monopolistic Competition, first coined in 1933 by Chamberlin, states that essentially, we can treat the market for generic drugs as one of monopolistic competition (Bellante, 2004). Within this theory for this current study, we assume that there is no free entry (barrier for money required for initial research and development, brand loyalty) and because of this, certain generic manufacturers with sufficient capital will continue to enter a market over a given period of time. This, in turn, affects the firm's decision-making. Entry in this industry affects the firm's demand curve by shifting the curve to the left, because a smaller quantity of the drug will be demanded at any given price. The demand curve is downward-sloping because the price that the firm expects to receive for its output will not remain constant as the firm increases

output of the drug. Using this model, we can assume a high cost of R&D for generic drugs, and as such, if fixed costs or marginal costs increase, then market entry will be smaller for a given quantity sold. The marginal cost will be handled as the additional cost of selling an extra unit, or dose, of the drug in this model.

Figure 1 (Taken from Grabowski, H. et al., 2007)

Graph showing a manufacturer's inverse demand and cost curves



Note: p = equilibrium price, m = marginal costs, qi*= firm's best response function where each manufacturer earns normal economic profits and entry ends*

Figure 1 above captures this by showing that entry in the market increases the number of manufacturers, until the point at which the manufacturer's inverse demand function is tangent to its average cost function. We also see from this figure that free entry increases the number of manufacturers until the point where each manufacturer's inverse demand function is tangent to its average cost function. After this point, the number of manufacturers will begin decreasing.

This is important to keep in mind, because even though we are not aware of drug manufacturer's cost or demand-side variables and can only theoretically infer, the framework of entry in the market increasing the number of manufacturers will only hold until a certain point. While the term m (marginal cost) must be smaller compared to the term F (fixed cost), Grabowski et al. (2007) justify using this model for pharmaceutical drugs.

While not fully generalizable, this study will endeavor to provide an initial step towards finding this price point in niche drug markets. By using this theoretical framework and assuming a model of monopolistic competition in our study, we can assume that increasing the number of manufacturers, as is allowed in free entry, would have to have the effect of lower prices (in this case to the point of earning "normal profit") for each manufacturer relative to their own cost function.

Using this theory, it is important to note that in the drug market, firms must then compete and differentiate drugs either through investment in R&D, increased variance in product lines (for different medical indications), increased number of indications for existing drugs, or higher investment in marketing strategy. This study will focus on analyzing the differentiation through increased number of indications, and analyzing how or whether this impacts drug pricing.

Data

The first primary data source used for this study will be the Center for Medicare and Medicaid's (CMS) Average Sales Price (ASP) data files for Medicare Part B Covered Drugs (See Appendix A). This data is panel data, consisting of a specific set of observations for a set of drugs, over a period of time. This full dataset contains the following inputs: HCPCS Code (used to identify drugs in place of scientific names and for insurance billing purposes), Short Description (name of the scientific form of the drug), HCPCS Code Dosage (CMS

recommended, standardized dosage for the drug), Payment Limit (Average Sales Price), Vaccine AWP (Average Wholesale Price) %, Vaccine Limit, Blood AWP%, Blood Limit (ASP limit for infusions), Clotting Factor (ASP limit for blood clotting factors), and Notes (additional notes about when data was updated, references).

The rationale for using this data is two-fold: 1. We can glean insights into Medicare Part B covered drugs, and how generic entry in the market affects prices of these drugs for Medicare patients, a growing population, and 2. Drug pricing data for generic or branded drugs is not available in any other form for public or academic use, leading us to the only large-scale time frame public use drug price data from the Centers for Medicare and Medicaid.

These data are available from 2005-2021, on a quarterly basis (January, April, July, October), for 635 drugs (data filtering process described below). Hence, price points from the point of entry of a drug to the endpoint measured are available 4 times annually. However, it is important to note that these prices, specifically for the indications to be analyzed in this study, rarely change within the same year, unless there is a drastic change in the market (i.e. COVID-19 pandemic)-- rather, the ASP change is seen in the long-run, as shown in the data discussed further below.

Data was filtered from this CMS ASP Excel file by first, creating our three categories (IBD, oncology antiemetics, and oncology immunosuppressants), and looking for any number of drugs within each of these categories. Some drugs had to be immediately excluded from the CMS ASP data due to being a vaccine or blood clotting factor, not a pharmaceutical drug. CMS Medicare Part B pricing data is limited to the years between 2007-2021, hence the 2021 time point was chosen to take the price of these drugs. Since only select drugs are Medicare-covered in the oncology and IBD categories, the n=21 drug sample size was landed at by filtering through

many insurance coverage documents (See Appendix C), to look specifically at Medicare Part B covered oncology antiemetics, chemotherapy drugs, and IBD drugs. From these, 40 drugs were found to cover the criteria of (1) being oncology and IBD drugs, and (2) having Medicare coverage, hence a guarantee that the ASP data would be publicly available. Out of these 40 drugs, only 21 had a most recent FDA label available, with the full indications listed on the label.

Some key limitations with this data include firstly, that it is rebate free data, meaning it does not reflect the price of the drug to a manufacturer, who will typically receive rebates for mass-producing the drug. It also does not reflect the price to consumers (or physicians/hospitals); rather the Average Sales Price reflects "the volume-weighted average of the manufacturers' average sales prices for all National Drug Codes assigned to the drug" (LII, 1995). Since most Medicare Part B data is rebate free, it is impossible to extrapolate the actual net price to manufacturers after discounts, statistics of which are rarely reported and hard to come by. Yet, we still must take into account 2 consequences of this rebate-free data: 1. Generalizability Problems (compounded by the fact that Medicare Part B data is used), and 2. Measurement Error. Hence, it is 1. Hard to generalize the results of this analysis to drugs not covered under Medicare Part B, even if they are in the same indications measured, and 2. We should attempt to thoroughly examine endogeneity/exogeneity issues to make sure to minimize these in our models. Endogeneity issues will be examined through preliminary correlation results, as well as through the use of an instrumental variable, market size.

The second primary data source used was the Drugs@FDA database. There are no consistent sources on the size of the database, though it is stated that it contains information about most drugs approved since 1939, with the "majority of information available for drug products approved since 1998" (FDA), and is updated daily. The complete database contains

FDA-approved labeling for human use products, therapeutically equivalent drug products (including generics), product information for patients (drug name, active ingredients, dosage form, route(s) of administration, strength), a product's approval history (approval letters, FDA reviews about safety and effectiveness), and regulatory information (drug application type, application number, approval dates, marketing status, submission classification) for drug products approved since 1998. From this, the following variables for a specific drug were filtered and collected: initial approval date, number of indications approved for currently, what each indication approved for currently is, number of indications approved for at initial approval date, and submission classification (for rare or orphan drug status). The type of indication for each drug will provide a control within each group, to account for drugs that may have been approved for indications that not all other drugs in each category are approved for. This gives us many of our data points necessary for independent variables to analyze, which will be discussed further in the section below.

One advantage of using this database is that the data given in terms of indications a drug is approved for, market entry, drug status, and drug route, are standardized across all drugs and reliable, as the FDA is legally bound to report this data. One concern with the Drugs@FDA database is that there has been, sometimes, few missing FDA approval labels for the year a drug was approved. Since this occurred with some drugs chosen, and no FDA label was available at all (inability to get number of indications, market entry time, etc), these drugs were removed from the sample.

Table 1

Summary of Variables Collected, Sources, Definitions, and Types

Variable Name	Data Source	Variable Meaning	Type of Variable
price	CMS ASP Drug Pricing Files	Manufacturer's average sales price of drug ($)	Continuous
marketentry	Drugs@FDA Database: System Entry	Years since FDA drug approval (from 2021)	Continuous
indexp	Drugs@FDA Database: FDA Label	Number of indications the drug is currently approved for - number of indications drug was approved for at initial approval time	Continuous
numind	Drugs@FDA Database: FDA Label	Number of indications the drug is currently approved for	Continuous
drugstatus	Drugs@FDA Database: System Entry	Rare or Orphan Drug status (=1; 0, if not)	Dummy
druggroup	CMS ASP Drug Pricing Files	Oncology anti-emetics (=1), IBD (=2), Oncology oral chemotherapy (=3)	Indicator
drugroute	Drugs@FDA Database: System Entry	Oral (=1), Intravenous infusion or injection (=0)	Dummy
patientsize	(See Appendix B)	Sum of patient size for each indication a drug is approved for	Continuous
patentexpiry	Pharmacompass.com	Years to patent expiry from 2021	Continuous

The price variable was included (current price of the drug for generic, incumbent firm as of October 2021) as the main dependent variable, and entry time (the years since FDA approval

to 2021, since this is the latest price data timepoint used for acquiring the price used) as the main independent variable due to the need for clear elucidation of the relationship between price and entry time. From the current literature, it is unknown as to whether or not newer generic entrants (later entry time) in the drug market have higher or lower prices compared to existing generic drugs on the market. Since there is information asymmetry between the firms and consumers, since firms more often than not have information much ahead of time on a competitor's FDA approval pipeline, it would not be expected that there is an immediate effect on price of a drug after FDA approval of a competitor's drug. Rather, we would expect to see either a rise or decrease in the drug price in the long-run.

The variable for number of indications was included as a control, due to much common literature that drug price is directly related to the number of indications a drug is approved for. Number of indication expansions was included because a growing literature suggests that more recently, drug companies increase the number of new indications a drug is approved for (through a less rigorous process than new drug approval) since the original approval, in order to justify price raises seen in recent years (Walsh et al., 2021). The effect of original indications vs. adding new indications could differ because smaller companies are now starting to use indication expansions as a way to use existing molecules in drugs to gain commercial exclusivity years (Viromii, 2019).

Number of biosimilars a drug is approved for could affect price as well, because if more substitutes exist for a drug on the market, the price of the generic could decrease, hence this is used as a control variable. Drug status, group, and route, are all included as dummy and indicator variables to signify whether or not a drug is an orphan drug, which group it belongs to (oncology or IBD), and which route it is administered (oral or intravenous injections), all of which can

increase the price, due to orphan drugs and intravenous injectables being more expensive, on average, than most drugs. While there are only 3 drugs with dedicated orphan drug status in this sample, this can greatly affect the price (and needs to be controlled for), as rare disease designated orphan drugs are more costly, whether to Medicare or the consumer.

Market size, for which patient size is used as a proxy for, is used as the main instrumental variable. Patient size is calculated as the sum of the patient population for each indication, in millions (for which there are more than 10,000 people, or > 0.005% of the population). This, as a proxy for market size, does not vary much over time (rather, there is much cross-sectional variation) hence is used to control for observed and unobserved confounding effects. Since patient size is exogenous in this model, it can help us to see the true correlation between market entry and price. Patient size can be a mechanism through which market entry time affects price, because as certain patient populations experience larger drug price increases in the market, this could affect the launch time of a drug, and hence, its price.

Patent expiry is defined as the years to the patent expiration of the drug from 2012, and this variable is included due to the patent expiry date's known relationship with price. As many drugs approach their patent expiry date and extend beyond it, their prices inevitably drop, as more comparables are available on the market and the prescribing behavior of physicians changes as the patent expires.

Table 2

Initial Summary Statistics for Variables Collected (standard deviations in parentheses)

Category	Mean Entry Time (Year)	Range Entry Time (Year)	Median Entry Time (Year)	Mean # Indication Expansions	Range # Indication Expansions	Median # Indication Expansions
IBD (n=6)	2004.8 (5.52)	14	2006.5	4.17 (1.83)	5	5
Oncology (n=15)	1990 (20.3)	62	1998	0.67 (1.06)	4	0
Pooled (n=21)	1994.5 (18.6)	62	1999	1.62 (2.09)	7	1

Table 3

Initial Summary Statistics for Variables Collected- contd.

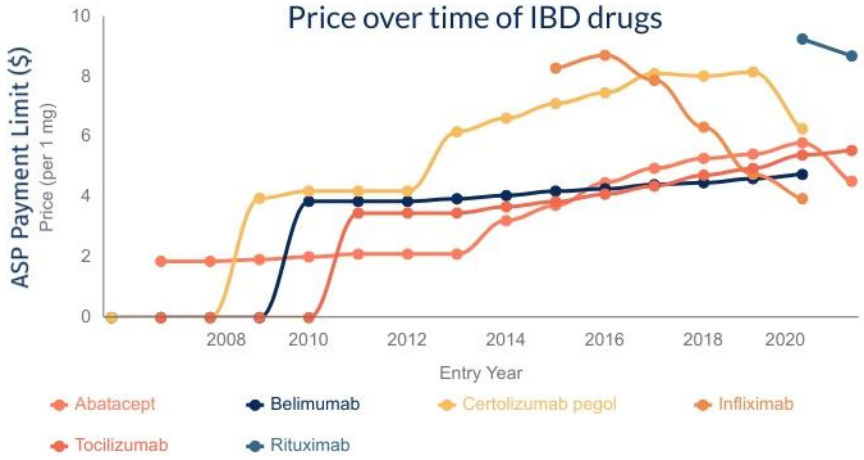
Category	Mean # Indications	Range # Indications	Median # Indications	Mean Price ($/mg)	Range Price ($/mg)	Median Price ($/mg)
IBD (n=6)	5.33 (2.07)	6	6	5.63 (1.71)	4.74	5.15
Oncology (n=15)	2.87 (1.55)	5	2	3.53 (6.78)	27.2	1.75
Pooled (n=21)	3.57 (2.01)	7	4	4.13 (5.82)	18.5	3.28

Initial statistics collected on entry time, indication expansions, number of indications, and price independent variables show considerable differences in some areas, such as range entry time, but this is to be expected, since a wide range of neweric generic entrants and older generics exist in both oncology and IBD. All other initial statistics seem to be in line with what the literature reports, as mean number of indication expansions for oncology are fewer, due to more specialized therapies being used, and mean indication expansions for IBD being the greatest

among the two categories, as this area is known to have drugs with multiple indication expansion (rheumatoid arthritis, ulcerative colitis, etc). Consulting with physicians who are specialists in these indications (rheumatologist and oncologist) to elucidate whether or not drugs included in each category are indeed competitors was done, and the comparability of drugs was confirmed.

Figure 2

Price over time of IBD drugs (n=6)



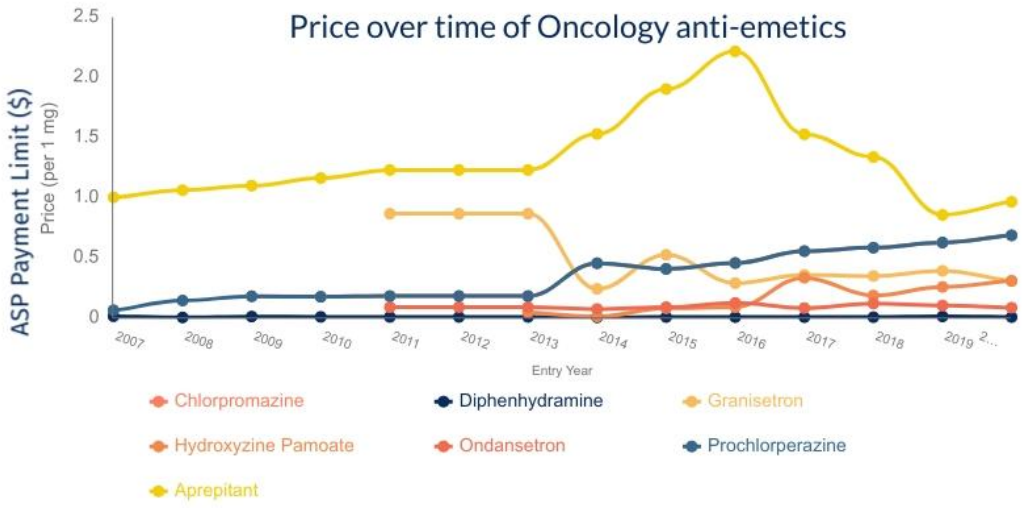
Note. Dosage was normalized to 1 MG, and the time period captured was from entry year-present.

Initial price change plots of IBD drugs show price steadily increasing over time, with later entrants in the market, coming in at higher prices. Rather than taking this at face-value, it is important to look at the reasons and further analyzes the reasons for the higher pricing and determine whether or not this is due to entry time, or rather, it is due to new indications approved for, disease burden of the indications, or number of biosimilars facing a certain generic. Some outliers include infliximab and rituximab, both of which are the only drugs in the sample which have approved biosimilars on the market, hence this could be leading to the higher prices seen

for these. A notable decrease in prices is seen in 2019-2020 onwards, indicating there might be legislation (Medicare Part B) that had an industry-wide effect, calling to the fore the need to analyze major policy shifts that could lead to overall price changes in the study.

Figure 3

Price Over Time of Oncology Antiemetic Drugs (n=7)



Note. Dosage was normalized to 1 MG, and the time period captured was from entry year-present.

Dissimilar to the price over time for IBD drugs, we see more stagnation over time of oncology antiemetics, inline with overall Medicare drug trends, since many Medicare Part B specialty drugs have not risen in price due to their niche patient populations and not being 'blockbuster' drugs with extremely high demand (Cubanski & Neuman, 2022). Outliers with higher prices include Aprepitant and Granisteron, which could be so due to their availability as an injectable therapy (in addition to oral). This underscores the need to control for drug routes (oral or injectable) when performing a regression. Since many of these drugs are used as immunosupressants after organ transplantation, in addition to chemotherapy uses, it could be

particularly useful to dive further into specificity of indications each drug is approved for, and include this information in the model.

Table 4

Correlation Matrix for Dependent and Predictor Variables

	entryt~e	price	indexp	numind
entrytime	1.0000			
price	0.4913*	1.0000		
indexp	-0.2537	0.3574	1.0000	
numind	-0.0316	0.3623	0.8283*	1.0000

The above correlation matrix in Table 4 shows a high positive correlation (>0.50) between number of indications (numind) and indication expansions (indexp) (statistically significant). The high correlation between indication expansions and number of indications could suggest a multicollinearity issue, where the data captured by the numind variable is also being captured by the indexp variable. Hence, the effect on the regression will be to drop the indication expansions (indexp) variable, instead using the number of indications variable (numind) as a predictor variable. The number of indications, as discussed before, has been shown in the literature as a possibly salient predictor of features such as drug price, whereas there has been no proven link between indication expansions and price (rather, only theoretical connections made), further motivating the choice to remove the indication expansions variable from the regression model.

Empirical Model

The main technique used to analyze this model will be a basic OLS regression. The main dependent variable to be analyzed in a regression will be drug price, taken from Medicare Part B ASP Data, as mentioned above. Given the overwhelming number of similar studies utilizing this

model for dependent price or other variables, a ln(price for drug) dependent variable seems to be logical. This will also be used to fix for heteroskedasticity and skewness in the data. The main predictor variable will be market entry time, and the following will be used as control variables: number of indications, indication expansions, type of indication, and patent expiry. Indicator variables include drug status, drug route, and drug group. The main instrumental variable used will be patient size (proxy for market size). Market entry will be measured as time of drug launch, or FDA approval date. This date was chosen in order to measure the effects of entrants' pricing relative to one another, rather than to one arbitrary, anchored time point. Advantages of this method include a consistent approval FDA timepoint always being available, but a disadvantage is having to include other parameters for changes in price from a fixed date (fixed effects model).

Number of indication expansions will be measured as the number of additional indications added on to the FDA label of the drug since the approval date. This is an important variable to look at, considering many pharmaceutical companies are now using indication expansions as a way to raise drug prices (Walsh et al., 2021). Equally important is the status of the drug, which will be a control, dummy variable assigned based on the FDA designations of rare, or orphan status. If the drug is approved for an indication that has rare or orphan status, this variable will have a value of 1, and if not, 0. The Drugs@FDA database will also provide information on the exact number of biosimilars approved for each drug. The indication type will be collected for each drug (each indication the drug is approved for), and a number from 1-n will be assigned for each unique indication.

Since many generics have multiple manufacturers, the first manufacturer (with the earliest FDA approval date, and hence, entry time) within the 2007-2021 range was chosen.

Some challenges with this include some drugs having approval dates before 1997, which poses a problem since ASP pricing data is only available starting in 2007. For the two drugs for which this is the case, the most recent ASP price data was taken. While this is not as accurate as if there was data for these early years, this adjustment had to be made due to data availability.

Figure 4

Initial Empirical Model Specification

$$(1)\ \ln(2021price) = \beta_0 + \beta_1(timing) + \beta_2(numberindications) + \beta_3(druggroup) + \beta_4(drugstatus) + \beta_5(drugroute) + \beta_6(patientsize) + \beta_7(patentexpiry) + \varepsilon_i$$

The coefficients will be interpreted as follows: β_1 will be analyzed as the percent increase or decrease in price ($) associated with a one year increase in market entry, β_2 will be the percent increase/decrease in price (in dollars) associated with a one number increase in number of indications, β_3 will be the effect of being in the oncology/RA group (druggroup = 1 if RA, =2 if oncology), β_4 will be the effect of being a rare/orphan drug status (rare/orphan = 1; 0, if not), β_5 will be the effect of being an oral pill or injectable (drugroute = 0 if pill, =1 if injectable), and β_7 will be the effect of an increase of one year until patent expiry for the drug.

Logging the price variable was determined to be the best course, as other studies regarding pricing have done this (Regan 2008; Grabowski et al. 2007), and this could fix heteroskedasticity problems in the data. Additionally, since drug prices have not been normalized by initial price in a year (changes in price relative to initial), this will be helpful. The regression will be run as a pooled regression to give us more robust data results, with the druggroup variable included as an indicator of whether the drug was in the oncology or RA group.

Variables such as market share were determined to have an endogeneity issue, since price and revenue are inextricably tied to market share, and the dependent variable in the regression, price. Patent litigation was also considered as a possibly salient variable, but ultimately, quantifying patent litigation proved to be difficult, and hard to standardize across drugs. Number of biosimilars a drug has could also be important to look at, but ultimately, only 3 generics in the data had approved biosimilars, and number of biosimilars might prove to be correlated with entry time and price of a drug, hence this covariate was not used in the model. Indication expansions were also dropped as a variable as described before, due to multicollinearity issues, since the number of indications is already included.

There are alternate approaches being explored to the dosage of the drug, which is currently standardized to 1 MG. It might be useful, in further revisions of the model, to include dosage as an independent variable, or covariate.

In addition to the model specification above, two different models will be used as robustness checks.

Figure 5

Robustness Check 1 Model

$$(2)\ \ln(2021price) = \beta_0 + \beta_1(timing) + \beta_2(numberindications) + \beta_3(timing * numberindications) + \beta_4(druggroup) + \beta_5(drugstatus) + \beta_6(drugroute) + \beta_7(patientsize) + \beta_8(patentexpiry) + \varepsilon_i$$

Model 2, above in Figure 5, will be a robustness check of Model 1include an interaction term between entry time and number of indications, since it is possible that the two of these predictor variables can have an effect together on price. This will serve as a check as to whether

or not entry time or number of indications themselves are salient predictors of price. We expected that the interaction term will be significant with regards to its effect on price because the number of indications could change in response to timing, which will consequently affect price of the drug.

Figure 6

Robustness Check 2 Model

$$(3)\ \ln(2021price) = \beta_0 + \beta_1(timing) + \beta_2(numberindications) + \beta_3(druggroup) + \beta_4(drugstatus) + \beta_5(drugroute) + \beta_6(patentexpiry) + \varepsilon_i$$

Model 3, above in Figure 6, will be a robustness check of Model 1, and not include the patient size variable. Since this variable is used as an exogenous instrumental variable in the original model, it is expected that timing and number of indications, the main two predictor variables, will not have a significant effect on price.

Results

Table 5

Regression results (Model 1 = original model, Model 2= Robustness Check 1, Model 3 = Robustness Check 2)

	Model 1 b/se	Model 2 b/se	Model 3 b/se
entrytime	0.068*	0.036	0.108*
	(0.03)	(0.04)	(0.03)
numind	-0.689**	-0.890**	-0.378
	(0.20)	(0.26)	(0.26)
druggroup	-1.256*	-1.351*	-2.315**
	(0.56)	(0.55)	(0.65)
drugstatus	2.831*	2.747*	1.229
	(0.91)	(0.90)	(1.10)
drugroute	-0.028	0.021	-0.556
	(0.70)	(0.69)	(0.96)
patientsize	0.052**	0.048*	
	(0.02)	(0.02)	
patentexpiry	0.003	-0.004	-0.041
	(0.05)	(0.05)	(0.07)
interact		0.009	
		(0.01)	
Constant	2.440	3.329	4.132*
	(1.35)	(1.54)	(1.77)
R-sqr	0.829	0.851	0.627
adj	0.709	0.719	0.424

* p<0.05, ** p<0.01, *** p<0.001

Regression results from the main model (Model 1) in Table 5 suggest that the strongest positive effect on price exists between entry time and price, drug status and price, and patient size and price. The significant result is that the variable of main focus, entry time, seems to have a positive correlation with price (significant at the 95% level), indicating that earlier generic

entrants (higher entrytime variable values) in these two indications have higher Medicare ASP prices. Specifically, a 1 year increase in entrytime, or a 1 year change from 2021, will result in a 6.99%[1] increase in prices.

The number of indications (numind) coefficient, significant at the 99% level, indicates that on average for an increase of 1 indication since approval of a drug, the price decreases by 49.79%. This is contrary to our hypothesis and current studies that say firms use greater numbers of indications to justify price raises of drugs. Another significant result is that the orphan status of a drug, on average, raises the price of the drug, due to the positive coefficient. This is expected as well, since orphan drugs are significantly more expensive, and for a niche patient population that typically needs it as a life-saving therapy. The patient size coefficient being significant at the 99% level signifies that it is possible that patient size could work to increase price either through earlier entry times, or number of indications.

The adjusted R-squared value of 0.7092 tells us that around 71% of variation is explained purely through the independent variables that affect the dependent variable, entry time. Since this is above 50%, this model clearly contains some salient variables that can explain effects in price, such as entry time and number of indications. However, there is room for improvement to increase the adjusted R-squared and goodness-of-fit by selecting different predictor variables in future iterations and studies; possibly, previously explored variables such as indication expansions or number of biosimilars.

The robustness check in Model 2, with the interaction term between entry time and number of indications, does not yield an entry time coefficient of significance, but it does still indicate that the number of indications has a significant effect on price. The interaction term does

[1] Coefficient was calculated as $=100*(e^{\beta}-1)$ for all coefficients

not have a statistically significant coefficient, leading us to believe that the interaction of these variables might not have a significant effect on price. However, the adjusted R-squared value is slightly higher than in Model 1, so it could be possible that including the interaction term better explains some variation in the price data than the original model. The robustness check in Model 3, with the patient size variable removed, gives us entry time again as a significant coefficient with effect on price; however, the effect seems to be much higher, indicating a 11.4% increase in price with an additional year in the market. This tells us that the patient size variable controls for some of the increase in price not explained by entry time. Number of indications is not significant in this model, indicating that patient size could be a mechanism through which the number of indications works to lower price; not just through entry timing. The adjusted R-squared value of 0.424 is much lower than in the other two models, showing that including patient size proved to be an important part of the original model specification.

Discussion

The positive and statistically significant coefficient on entry time in the original model means that newer entrants have lower prices than earlier entrants in these markets. This expected result in line with our original hypothesis and theoretical framework is significant, and could tell us that there is a negative relationship between the growing number of competing drugs in the market, as time goes on, and price. One possible mechanism that could explain this is that since the number of substitutes increases for a drug during a given period of time, the price of the drug decreases during the same period. This can be explained by the fact that with more firms competing in a market with comparable drugs, the price will decrease naturally over time.

There could be a few possible explanations for the surprising result of a negative and statistically significant coefficient on the number of indications. One, the oncology and IBD drug

firms for the drugs specifically analyzed could be adding indications to attract vastly different and new customer bases (in other indications), where the overall price is lower. There could also be a complex industry-wide strategy used by generic competitors in this market that involves increasing indication numbers only to extend drug exclusivity rights in the short-run, and possibly only raising prices in the long-run.

The significance of patient size as a mechanism, or instrument, through which both entry time or number of indications could exert their effect on price is of importance. Since patient size is relatively stable over time (specifically for the sample size of indications collected in this study), and not one prone to fluctuations over time, there must be something endogenous to the disease indications each drug is approved for that affects number of indications and entry time, and hence, price. This should be further studied by closely analyzing how the types of indications (acute, chronic) a drug is approved for and overall market trends in these indications could be closely connected to a firm's decision-making with regards to entry timing and price.

The results on entry time as significantly impacting price could have implications for pharmaceutical market policy. If the current work is confirmed by future studies similar to this studying entry time and price in the generic pharmaceutical market, it is possible that future drug policy should focus on promoting competition within the pharmaceutical market to lower generic prices. As more generic entrants are encouraged through things like subsidies and public policy, this can prevent the rise of extremely high-priced blockbuster drugs put out by a few companies with a monopoly. Even as the FDA's median review times for new drug applications are decreasing (Advisory, 2020) and more generics are approved each day, it is important to note that "more than 500 brand drugs still lack competition, even though there are no patent protections or periods of exclusivity that would prevent the approval of competing generic versions…These

"sole source" products are most at risk for price spikes" (Pew Charitable Trusts, 2019). Promoting competition in the overall drug market, and specifically promoting research and development in the generic drug market could prevent these price spikes seen recently.

Limitations and Future Directions

One of the biggest limitations with the study that could be improved in future iterations is the small sample size of n=21 drugs. The constraint of finding Medicare ASP prices for all the drugs available, as well as intact FDA labels and updates proved to be a large problem, as more than 20 drugs had to be cut from the sample due to these issues. In future studies, it would be beneficial to raise the sample size to as high as possible within these drug categories, and possibly expanding outside of oncology and IBD drugs to fully capture the extent of the effect found in this paper to the full drug market. It would also be beneficial, if possible, to use other types of pricing data (other than Medicare and Average Sales Price data), so that we can look more closely at non-Medicare consumer, physician, or manufacturer prices. This will increase the generalizability of the results of this current study. Another limitation arose from inconsistent sources for the patient size data, which could have led to some measurement error in the instrumental variable. While the process of accruing patient size data was novel and unique, if possible, future iterations of the study should standardize the process of finding patient size for each drug, both in sources used, and methodology for doing so.

Further regressions and studies must be performed to follow up on these results and verify the generalizability and accuracy to other drugs in the generic market. These could include increasing the drug markets to include some large patient areas such as cardiology, diabetes, and other chronic conditions. With heart disease, diabetes, cholesterol, and blood pressure being some of the top-ranking diseases for which drugs are prescribed in the U.S. today (Wallach,

2021), the high patient burden and economic burden (in terms of rising prices) in the U.S. will need to be further analyzed through the lens of generic drug prices and competition. This model could also be fine-tuned and analyzed by looking at how exactly the drug launch timing of direct competitors of generic products (branded and biosimilar drugs) affects the price of the generics. This could help to elucidate the mechanism by which entry time affects price in the generic market currently.

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Appendix A

Medicare Part B covers a limited number of outpatient prescription drugs, and these are usually drugs that are given in a doctor's office, or outpatient hospital setting. Many drugs selected for analysis in this study (RA or oncology) are injectables/infusions, hence they are covered under Medicare Part B (Medicare, 2021). Medicare Part D covers a wider range of prescription drugs, while Part B is for more specialized cases. Since many of the drugs analyzed in this study are approved for some niche indications, and mostly all are injectables, Part B covers them.

Part B pricing dynamics are as follows: "Existing Part B rules strictly limit the ability of CMS[2] to either lower prevailing market prices or act to influence drug utilization. Medicare bases Part B reimbursement on ASPs, which reflect the average of actual (net) US prices for a drug and include all price concessions such as discounts and rebates. Updated by CMS every quarter, ASPs incorporate sales data (with a two-quarter lag) that manufacturers must report, consistent with detailed CMS instructions. Medicare reimburses providers for the cost of acquiring a drug and pays a separate fee for administering the drug" (Lieberman & Ginsburg, 2019). From this, it is important to keep in mind that the pricing data used is rebate-free, and does not at all reflect the price-to-consumer, due to consumers paying a separate Medicare premium. Hence, the ASP pricing data used reflects and highlights manufacturer pricing dynamics.

[2] (Center for Medicare and Medicaid Services)

Appendix B

Since patient size is not available for each drug on any standardized source, the method used to determine the patient size is as follows: 1. Each drug's indications were listed out and coded in the *indication* variable, 2. The patient size for each individual indication was found through various academic and institutional sources (listed below) for the U.S. in the most recent year, 3. When this was not available readily, the prevalence rate of the specific disease was multiplied by the number of people with the broader disease to get the total number of patients with the disease, 4. This number was totaled (summed) to get the final patient size number, and 5. Indications for which there were below 10,000 people in the U.S. who currently have it were excluded from the total patient size count due to the miniscule contribution of an indication with a 10,000 people patient size (<0.005%).

Sources Used for Patient Size Info

1. (https://www.cdc.gov/arthritis/data_statistics/national-statistics.html)
2. https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Juvenile-Arthritis
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Appendix C

List of sources from which Medicare-approved Oncology and IBD drugs was extracted:

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4. https://www.healthpartners.com/insurance/medicare/part-d-prescription-drug-coverage/formulary/
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Data Sources

1. CMS Data downloaded from: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice
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