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POLICY BRIEF

The Impact of Price Setting at 9 Years on Small Molecule Innovation Under the Inflation Reduction Act*

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Abstract

This policy brief provides a quantitative analysis of how the Inflation Reduction Act's (IRA) policy to set prices for select small molecule drugs 9 years after FDA approval impacts innovation and patient health. Price setting under the IRA undermines existing intellectual property laws, reducing incentives for investment in research and development (R&D) that discovers new drugs and identifies new uses and populations who can benefit from already-approved drugs. We conservatively find that the IRA's policy to set prices at 9 years after market entry for select small molecule drugs will reduce their expected revenues in the U.S. market by 8.0%, which implies a reduction in R&D investment of almost 12.3%, or $232.1 billion over 20 years. Over the same time frame, we conclude that there will be 188 fewer small molecule treatments, including 79 fewer new small molecule drugs and 109 fewer post-approval indications for these drugs. We find that this forgone innovation is expected to lead to 116.0 million life years lost due to the missed opportunities to improve health. We believe these estimates of foregone innovation are conservative due to several factors driving revenues even lower than analyzed here but for which credible data sources are lacking.

Section 1: Introduction

Current U.S. laws state that patent protection generally lasts for 20 years from the time the patent application is filed. However, because a large amount of this time is spent on clinical development and regulatory review for drugs, the actual remaining patent life at the time of approval is much less and highly variable across drugs. Today, the average number of years at which generics typically enter the market is 12 to 14 (Grabowski et al., 2017). In addition to patents, U.S. intellectual property protections for prescription drugs include regulatory exclusivities governed under the Hatch-Waxman Act. These protections have successfully balanced incentives for innovation with an abbreviated pathway for generics, which now command more than a 90 percent share of all U.S. prescriptions. Beyond promoting generic competition, these robust innovation incentives have led to brand-to-brand competition that puts downward pressure on prices even prior to generic entry.

The recently enacted Inflation Reduction Act (IRA) upends this framework and existing incentives for biopharmaceutical innovation. The IRA includes provisions allowing the government to set prices for select medicines at 9 years after FDA approval for small molecule drugs (generally drugs that come in pill and tablet form) and 13 years for large molecule (biologic) medicines. While the law refers to the process of determining prices through negotiation, there is no room for manufacturers to reject the price set by the Centers for Medicare & Medicaid Services (CMS). For small molecule drugs, this policy significantly shortens the time for manufacturers to earn a return on their investment—including for the initial research and development (R&D) to discover and develop a new drug and the R&D that takes place after a drug is approved for new uses and populations.

The disproportionate impact that the IRA is likely to have in disincentivizing innovation in small molecule drugs is particularly concerning given that small molecule drugs provide critical, unique benefits to patients. Small molecule drugs are essential to treat therapeutic areas such as cancer (since only small molecules can penetrate cell membranes to target cancerous cells) and mental health (because only small molecules can penetrate the blood brain barrier). Small molecule drugs also allow for a variety of treatment options in different forms. Indeed, their composition and stability allow them to be easily reproduced and drive a robust low-cost generics market. Many of these traits improve patients' access and adherence to medicines, particularly for populations with otherwise poor access to care.

When the IRA was passed by Congress, the Congressional Budget Office (CBO) estimated that the law would lead to merely 15 fewer new drugs brought to the market over 30 years. Since then, the CBO's approach has been widely criticized as a significant underestimate of the true effect of the IRA on R&D investments and future innovation. Specifically, this estimate ignores the disproportionate effect on small molecule drugs due to reducing the time to earn potential returns from an average of 12-14 years before generic entry to just 7 years before products are selected for price negotiations and 9 years before the maximum fair prices (MFPs) are set.

Additionally, the CBO ignores the nature of biopharmaceutical R&D and how therapeutic value increases over time. The CBO's approach fails to capture the implications of the reduced time to earn returns on R&D invested after a drug is approved to identify new uses. This post-approval research leads to additional FDA approvals for new dosage forms or uses in new patient populations, e.g., pediatric patients; different stages of disease; and in many cases, completely different diseases. For many therapeutic areas, including cancer, much of the improvement in survival rates and other outcomes stems from post-approval clinical trials. For example, one drug approved by the FDA to treat melanoma in 2014

is now approved to treat 20 different types of cancer identified in post-approval research (USC Schaeffer Center, 2023).

In this analysis, we aim to better inform the magnitude of the effect of the IRA's price setting provisions on innovation by considering the implications of the shortened time period for small molecule treatments on revenues before being subject to price setting at 9 years post-approval. The IRA effectively reduces the period manufacturers have to earn revenue based on the market prices by nearly 40%, from a pre-IRA average of 12 to 14 years to a maximum of 9 years.

To illustrate the potential effects of this shortened revenue generation period, we first estimate the revenue associated with a drug's initial approval – using the simplified assumption that the revenue period for the initial indication(s) extends from the product's approval to the expiration of the patent selected for patent term restoration as a proxy. This approach understates the total market exclusivity period of the drug but allows us to approximate the revenues associated with the first indication and then separately model the additional revenue associated with new indications beyond the first indication.

To model the impact on post approval indications, we use information on historical patterns of FDA approvals for small molecule drugs and evidence from the literature. First, available data (PHAR, 2022) suggests that 52.1% of small molecule drugs receive approval for additional indications after initial FDA approval. Our analysis considers a range between 15% to 25% of added revenue per new post-approval indication lost due to the IRA.

We conservatively find that the IRA's policy to set prices at 9 years for small molecule drugs will reduce expected revenues generated by small molecules in the U.S. market by 8.0%, which implies a reduction in R&D investment of almost 12.3%, or $232.1 billion over 20 years. We find that this will lead to 188 fewer small molecule treatments over the next 20 years, including 79 fewer new molecules and 109 post-approval indications. We find that this forgone innovation is expected to lead to 116.0 million life years lost. Estimates of this foregone innovation is conservative in the sense that no spillovers to private markets outside Medicare are assumed.

This policy brief is outlined as follows. Section 2 discusses the IRA's impact on reducing the reward period for small molecule drugs. Section 3 estimates the revenue and implied R&D effects, as well as the reduction in new drugs and patient health, considering lost revenue for the initial drug approval during the reward period and lost post-approval revenue. Section 4 concludes and discusses why these estimates of foregone innovation are conservative due to several factors driving revenues even lower than analyzed here but for which credible data sources are lacking.

Section 2: The Impact of the IRA on the Reward Period of Successful Small Molecule Drugs

Small molecule drugs are drugs that have a low molecular weight, are typically given orally, work within and outside of cells, and are distributed to the organs and tissues (NCI, 2022). Small molecule drugs represent important treatment options for patients for several reasons. First, their small size allows them to enter cells easily and cross the blood-brain barrier, enabling them to reach targets that large molecules typically cannot and thus treat cancer and neurological disorders (Banks, 2009). Second, they are highly stable and can be easily stored and taken at home, which provides greater convenience for patients since the medicines are usually available at the pharmacy counter, versus those drugs that must be administered in a doctor's office or hospital. Third, small molecule drugs can be produced in many dosage forms, optimizing convenience and adherence for a wide range of patient populations (FDA, 2022). Studies show that increased medication adherence reduces avoidable emergency room visits and other health care costs (Philipson and Di Cera, 2022). This means that adherence from small molecule drugs can result in cost offsets elsewhere in the health care system. Fourth, given their composition, stability, and the well-established regulatory pathway for their approval, small molecule drugs can be reproduced more readily as generics, providing unique benefits to patients and the health system because generics are available at a significantly lower cost.

Over time, small molecule drugs have continued to dominate in new drug approvals by the FDA. According to the FDA Center for Drug Evaluation and Research (CDER, 2022), among all New Molecular Entities (NMEs) approved from 1985 to 2021 where small molecule drugs were approved under New Drug Applications (NDA), 81.7% (or 980 out of 1199) of approved NMEs were small molecules. Specifically, in 2021, 72% (36 of 50) of approved NMEs were small molecules, as shown in Figure 1. Given the prevalence and importance of small molecule drugs, it is of great significance to investigate the potential impact of IRA cuts in the reward period on small molecule R&D innovation and gain insights into the implied reductions in new drugs and patient health benefits.

Figure 1: Number of Small Molecule Drugs Approved as New Molecular Entities by the FDA, 2010-2021
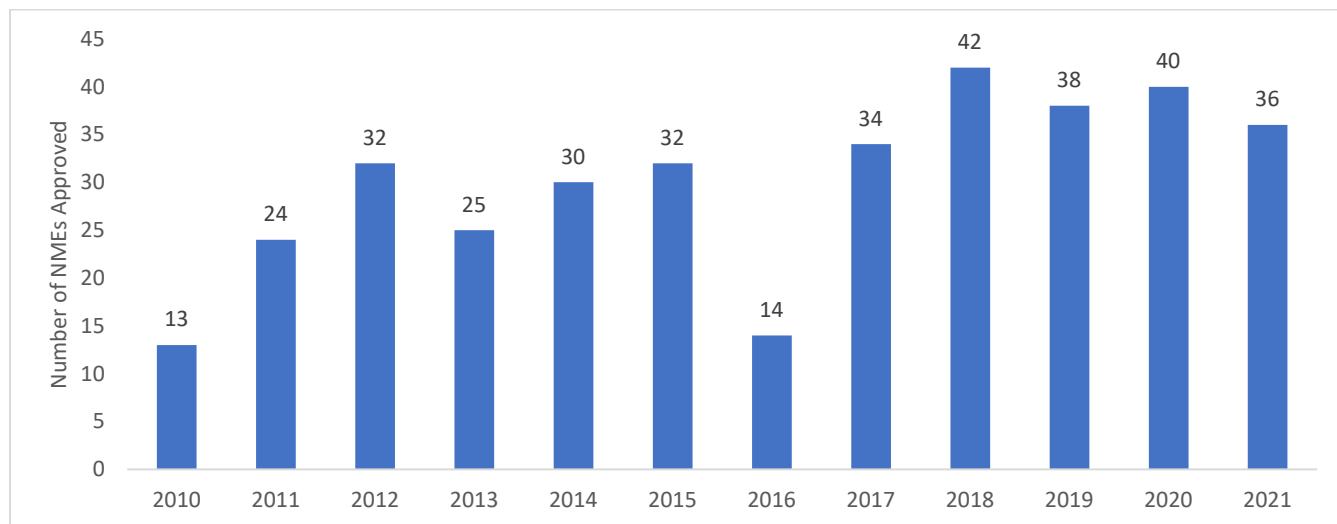
Section 2.1 The Reward Period for Top Selling Small Molecules

The amount of time a drug has on the market prior to generic entry is an important factor influencing R&D investments because it takes many years to recoup the R&D costs and earn a positive return for a new drug introduction. In fact, because only a fraction of drug candidates entering clinical trials are approved (DiMasi et al., 2016), and only a fraction of approved medicines generate revenues that exceed the average cost of bringing a medicine to market (Vernon et al., 2010), companies will only continue to invest in R&D if expected returns from these few financially successful products are sufficiently large to make up for the many "failures."

A brand drug's primary source of protection from generic entry comes from patents. Since manufacturers file for patents on pharmaceutical products at the beginning of the clinical development process but the patent term is counted from the application date, significant patent time is lost by the time of FDA approval. This results in a significant reduction in the effective life of a drug patent compared to the overall patent life of 20 years; As a result, small molecule drugs have averaged 12 to 14 years from launch to generic entry (Grabowski et al., 2021). The IRA further shortens this reward period.

We use patent information to quantify the impact of the IRA's reduction of this important period of economic returns from a new drug, which we will refer to as the "key returns period." We investigate the distribution of key return periods for the initial approval of top selling small molecule drugs. We first define top-selling products as those that have U.S. sales over $1 billion in 2021. According to the annual reports of pharmaceutical companies and J. Chem. Ed. (2021), 95 small molecule drugs meet this benchmark. Second, we get information about patent expiration dates and extensions for each drug from the FDA Center for Drug Evaluation and Research Orange Book (FDA, 2022a). The key returns period is determined as the time range between the FDA's first approval date (i.e., the date of approval for the first indication or indications of the drug) and the relevant patent expiration date. If multiple patents exist for a particular small molecule drug in the Orange Book and the drug has a patent that received patent term restoration, we focus on the patent chosen for patent restoration. This is the restored primary form of patent protection on the molecule itself and the patent typically chosen for Hatch-Waxman extensions.
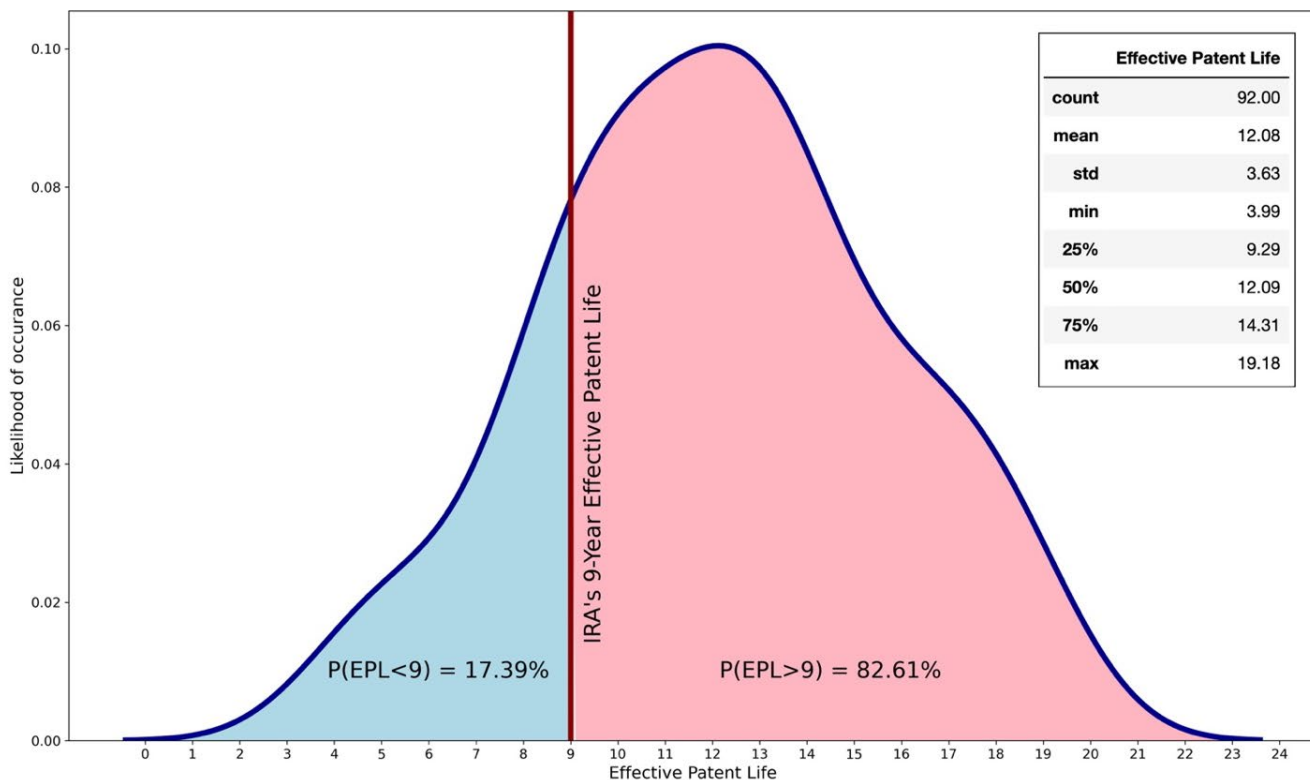
Using our metric, a small molecule drug had an average key returns period prior to the Inflation Reduction Act of 11.82 years, with a standard deviation of 3.42 years. Our approach of measuring the regulatorily-defined reward period differs from other measures of exclusivity durations based on product launch dates and entry of generics, such as market exclusivity period (MEP) (Grabowski et al., 2021). Those other exclusivity measures may better capture added exclusivity from additional patents as well as through regulatory exclusivities such as pediatric exclusivity extensions. While our approach may not capture the entire period of exclusivity ultimately achieved, we nevertheless attempt to capture the additional revenues generated by any post-approval indications, as described later.

Section 2.2 The Impact of IRA on the Key Returns Period for Top-Selling Small Molecule Drugs

Under the Inflation Reduction Act (2022), small molecule drugs without generic or biosimilar equivalents covered under Medicare Part D or Part B that are also among the highest-spending Medicare-covered drugs and are nine or more years from FDA approval will be eligible for price setting. The number of selected drugs is limited to 10 Part D drugs in 2026, another 15 Part D drugs in 2027, another 15 Part B and Part D drugs in 2028, and another 20 Part B and Part D drugs in 2029 and later years (CMS, 2022). Over the first 5 years of the price setting program, the 100 Part D and B drugs expected to have their prices set represent almost half of current Medicare drug spending (Avalere, 2022).

Retrieved from the CMS Medicare Spending by Drug (2022) and the FDA Center for Drug Evaluation and Research Orange Book (2022a), we determine the small molecule drugs that are most likely to be price set in the future. This is according to the criteria of Medicare-covered drug spending and FDA approval years based on the IRA statute. We then identify 92 small molecule drugs with sales over $1 billion in 2021 and plot the fitted distribution of their key return periods in Figure 2 (3 drugs are excluded because of data availability). As mentioned above, the key returns period is calculated as the difference between their patent expiration dates and FDA approval dates, measured in years and rounded to the second decimal. We find that the key returns period of these top-selling small molecule drugs is 12.08 years, with a range from 3.99 years to 19.18 years, as shown in Figure 2. Among these, 82.6% have a key return period longer than the IRA's 9-year benchmark. This suggests that the IRA would effectively shorten the key returns period of the majority of small molecule drugs, leaving less than 20% unaffected. Specifically, for 25% of drugs, the IRA cuts the key returns period by 5.3-10.2 years.

Figure 2: Distribution of Key Returns Period for Top-Selling Small Molecule Drugs Identified

Effective Patent Life	
count	92.00
mean	12.08
std	3.63
min	3.99
25%	9.29
50%	12.09
75%	14.31
max	19.18

P(EPL<9) = 17.39%   P(EPL>9) = 82.61%

Source: FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)
Note: This distribution figure is for the 92 top-selling small molecule drugs in the U.S. that had annual sales over $1 billion in 2021. The key returns period of a drug is defined as the time range between the FDA's first approval date and the patent expiration date. If multiple patents exist for a particular small molecule, we focus on the patent of the molecule itself. For products with a patent receiving patent term restoration, we focus on the patent chosen for patent restoration. This figure displays the fitted density rather than the actual histograms of the data points.

Section 3: The Revenue and R&D Effects of the IRA

In this section, we estimate the revenue effects of the IRA, including the revenue effects on initial indications and post-approval indications and the consequent R&D effects. To arrive at reduced R&D investment, we first estimate the percentage reduction in revenue with the IRA essentially cutting the key rewards period to 9 years and apply the percentage reduction in R&D elasticities based on the literature. Given that the IRA targets the Medicare market, we assume all these R&D reductions occur inside of Medicare. However, it is possible that the government-set price will spill over to the commercial market, making our estimate a lower bound.

Considering only the direct revenue effect of initial indications due to shortening the key returns period, we project that the present value of revenue in the Medicare market will decrease by 13.9%. In addition, if we take into account the revenue effect of discouraging post-approval indications, assuming each post-approval indication contributes an additional 15%-25% of total revenue for the drug, we estimate that the present value of revenue in the Medicare market will decrease by up to 26.6%. Multiplying by the 30% that accounts for the share of the total U.S. retail prescription drug spending paid by Medicare, we estimate that the revenue will reduce by 4.2% (only direct revenue effect), and up to 8.0% (plus post-approval revenue effect) in the U.S. market.

Combining with current R&D levels, we then infer the absolute reduction in R&D and translate it into the number of life years lost based on the reported correlation from the literature. Using an average R&D elasticity of 1.54 (Philipson and Durie, 2021), the IRA yields an R&D reduction of 6.4% considering the direct effect, and a reduction of 12.3% considering direct and post-approval effects. With the counterfactual small molecule R&D investment attributed to the top selling drugs for the next 20 years estimated to be $1.9 trillion, considering only the direct effect of initial indications due to shortening the key returns period, such a reduction will decrease R&D by $121.4 billion, leading to a 60.7 million reduction in life years valued at $6.1 trillion to $29.7 trillion with varying VSLY from $100,000 to $490,000, where the latter is the average VSLY across the literature reported in Philipson and Durie (2021b). Adding the revenue effects of discouraging post-approval indications, R&D investment will decrease by $232.1 billion for the next 20 years, resulting in 116.0 million less life years valued at $11.6 trillion to $56.9 trillion with a VSLY from $100,000 to $490,000.

Section 3.1 Revenue Reduction for Top-Selling Drugs

We examine the revenue impact of the IRA on top-selling drugs considering initial approval and follow-on approvals separately. Focusing solely on initial approvals, we estimate a 13.9% reduction in revenue for the top-selling drugs in the Medicare market, yielding a 4.2% revenue reduction in the whole U.S. market. Taking post-approval indications into consideration, we arrive at a range of 21.5% to 26.6% of revenue reduction depending on the fraction of revenue from post-approval indications, leading to a 6.5% to 8.0% reduction in the revenue for the entire market.

3.1.1 Revenue Reduction Associated with Drugs' Initial Indications

To estimate the impact of the IRA price setting provisions on revenue, we first estimate the percentage reduction in revenue associated with drugs' initial indications by cutting the key returns period in terms of the overall expectation of present values. We start from the perspective at the start of drug development and estimate the revenue that would be achieved without the IRA as the counterfactual with the following equation. In the equation, x stands for the years following patent application spent in development, and T stands for the total years of patent life (typically 20 years), resulting in $T - x$ being the key returns period.

$f(T - x)$ refers to the frequency of the key returns period within the sample, which we rounded to 0.5 years for clearer frequency calculations. For example, for a drug with a key returns period of 13.47 years, we round it to 13.5 years. If there are ten drugs, and two other drugs also have 13.5 years after rounding, then $f(T - x) = f(13.5)$ would equal 30%. Thus, the first summation essentially represents the calculation of expectations. The second summation refers to the calculation of present values, where we assume there is no revenue in the drug development stages and after the key returns period. β represents the annual discounting factor, and E represents the annual earnings, which we assume to be identical across the years and key return periods. The former part of the assumption (across years) is highly conservative as revenues generally rise throughout the life of a brand medicine as provider, patients, and the health care system become more familiar with it. The latter part of the assumption (across products with different key return periods) can be viewed as estimating expected present revenues before the development time of one drug is known, where the identical revenue assumption can be sustained. Since we measure percentage reduction in the end, this assumption is reasonable as they cancel out in the division.

$$V = \sum_{x=0}^{T} \left[f(T - x) \sum_{t=x}^{T} \beta^t E \right] \qquad \text{3.1}$$

For revenue under the IRA, we adopt a similar equation, with the key difference of cutting off earnings after year 9. This design corresponds to the IRA's 9-year price setting term, where a drug either obtains earnings for the entirety of its key returns period or over 9 years, whichever is smaller.

$$V_{IRA} = \sum_{x=0}^{T} \left[f(T - x) \sum_{t=x}^{\min \{T, x+9\}} \beta^t E \right] \qquad \text{3.2}$$

With the two equations, we calculate the percentage reduction by taking the difference between the two present values and dividing the difference by the counterfactual present value. As previously stated, our assumption about equal earnings allows us to estimate the percentage reduction with only the discounting factor and time.

$$\begin{aligned} \textit{Revenue Reduction \%} &= \frac{V - V_{IRA}}{V} \\ &= \frac{\sum_{x=0}^{T} [f(T - x) \sum_{t=x}^{T} \beta^t E] - \sum_{x=0}^{T} \left[f(T - x) \sum_{t=x}^{\min \{T, x+9\}} \beta^t E \right]}{\sum_{x=0}^{T} [f(T - x) \sum_{t=x}^{T} \beta^t E]} \\ &= \frac{\sum_{x=0}^{T} [f(T - x) \sum_{t=x}^{T} \beta^t] - \sum_{x=0}^{T} \left[f(T - x) \sum_{t=x}^{\min \{T, x+9\}} \beta^t \right]}{\sum_{x=0}^{T} [f(T - x) \sum_{t=x}^{T} \beta^t]} \end{aligned} \qquad \text{3.3}$$

Based on our aforementioned distribution of drug key returns periods, we use a discounting factor of 0.9 to estimate the percentage reduction of 13.9%. Using a discounting factor of 1, which does not diminish the weights associated with future years, the percentage reduction equals 22.6%. While this percentage may seem small compared to the 80% integral for drugs with a key returns period larger than 9 as shown above, it must be noted that the plotted distribution spikes around a key returns period of 12 years, suggesting a reduction of 25% and that drugs with a key returns period greater than 9 years can still accumulate earnings in the first 9 years. To corroborate this percentage, we also present the distribution

of lost key return period percentages below. As is shown in Figure 3, after rounding to the nearest 0.5% (for example, 32.2% to 32% and 32.4% to 32.5%), the peak of the distribution for drugs with key returns period loss is around 30%, while drugs without key returns period loss (at 0%) take up a substantial fraction.

With the estimated 13.9% reduction in revenue in the Medicare market, we then multiply Medicare drug volume sales as a share of total U.S. sales to get the corresponding revenue reduction in the entire U.S. market. As reported by the Kaiser Family Foundation (2019), Medicare's share of the nation's retail prescription drugs is approximately 30%. Using this number, we arrive at a 4.2% revenue reduction in the whole U.S. market.

Figure 3: Distribution of the Percentage Loss of Key Returns Period for Top-Selling Small Molecule Drugs Identified
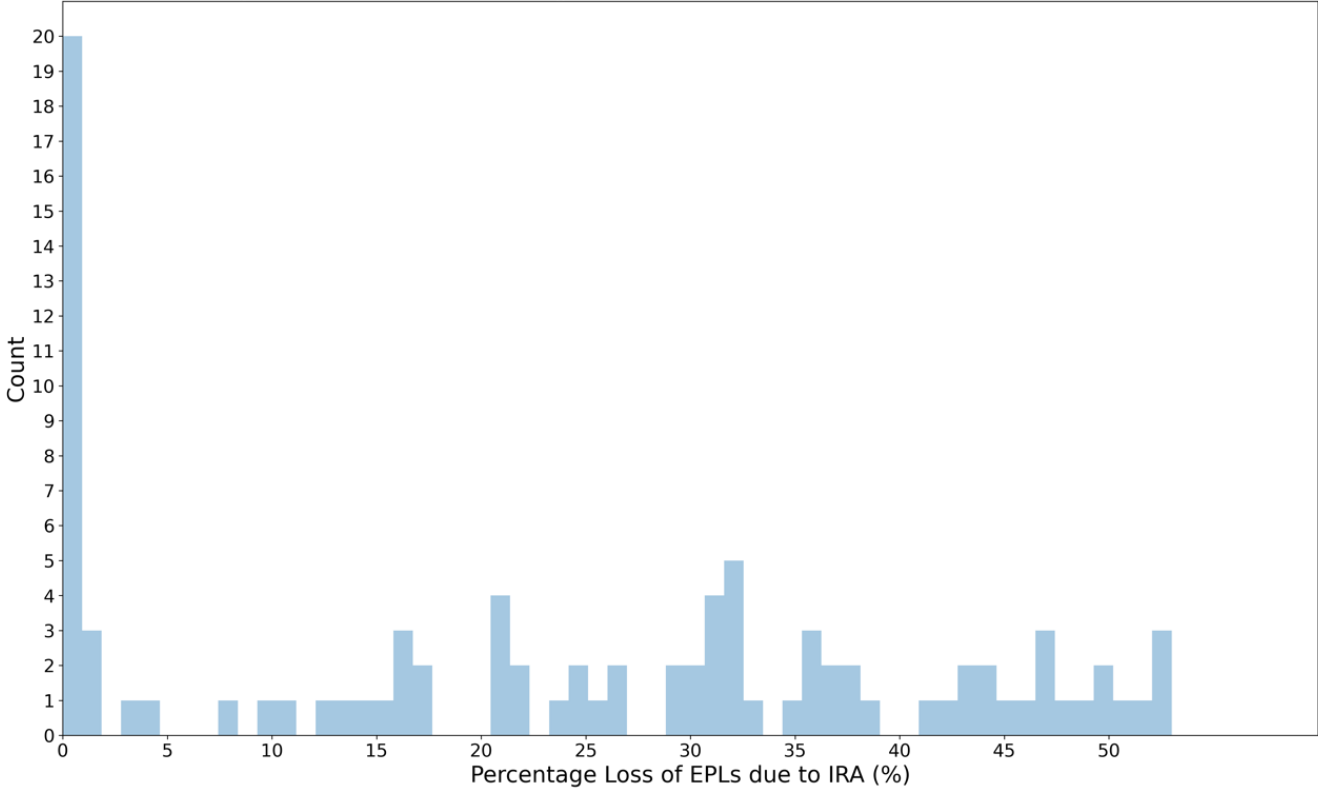

Section 3.1.2 Revenue Reduction Considering Post-Approval Indications

In addition to the direct revenue effects of the IRA on initial indications by cutting the key returns period of small molecule drugs, another important pathway leading to potential revenue reductions is that the IRA will further impact post-approval R&D investment which produces additional indications (i.e., new uses) for these top-selling drugs. To quantify the magnitude of this indirect effect, we estimate the average share of reduction in post-approval indications under the IRA.

According to the Partnership for Health Analytic Research (PHAR, 2022), post-approval indications are common throughout the life of the drugs studied, where 52.1% (37 out of 71) of small molecule drugs received at least one additional indication after their initial approval. Among the total 47 medicines identified as having additional approvals, 53 post-approval indications were approved more than 7 years after the initial approval, as shown in the green area in Figure 4. The frequency of approvals for these

post-approval indications based on this study implies an average reduction of 1.1 post-approval indications per drug due to the IRA if we assume that companies would no longer develop new indications beyond 7 years after initial approval. This is a conservative estimate, because a post-approval indication approved at the end of year 7 (when drugs are selected for price setting) would only have two years to generate revenues before government-set prices go into effect. For context, the PHAR data show that each new molecule has a total of 1.4 additional post-approval indications.

Figure 4: Timing of New Indications Approved Following Initial FDA Approval Among All Medicines Initially Approved from 2010 to 2012
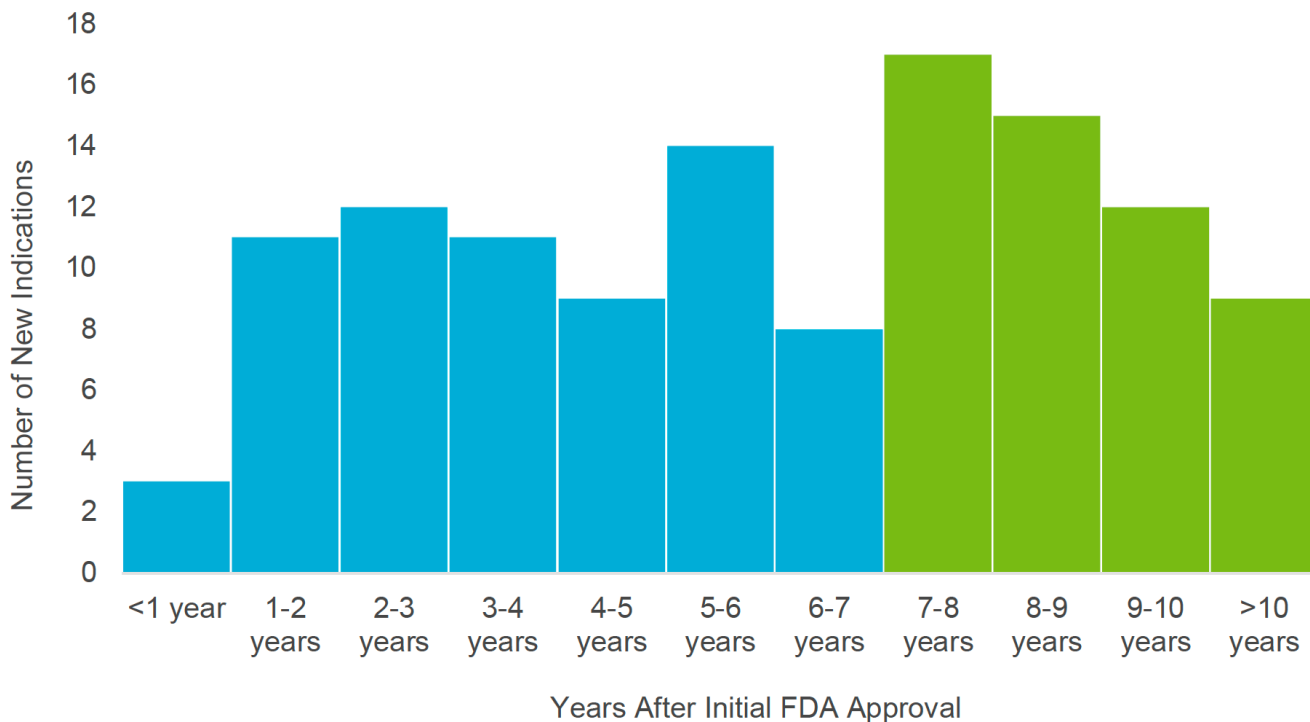
Source: Partnership for Health Analytic Research (2022)

In the previous section, we created formula (3.3) for the direct revenue effect of cutting the key returns period by taking the difference between the present values of top-selling drugs' revenue with and without the IRA, and then dividing by the counterfactual present value without the IRA. Assuming all top-selling small molecule drugs have universal distribution patterns of post-approval indications, and their revenue is evenly distributed across each indication (i.e., each post-approval indication has the same marginal revenue), we set our estimation that each post-approval indication accounts for 15%-25% of the total revenue of a drug. We denote $\gamma = 52.1\%$ as the share of small molecule drugs that received additional indications after initial approval, $\Delta I = 1.1$ as the average number of lost post-approval indications impacted by the IRA, $15\% \leq \alpha \leq 25\%$ as the estimated revenue reduction corresponding to the loss of each post-approval indications, and V_{IRA_F} as the present value of top-selling drugs' revenue with a reduction in post-approval indications under the IRA. From this, we derive the percentage revenue reduction due to shortening the key returns period plus discouraging post-approval indications, as shown in formula 3.4:

$$Revenue\ Reduction\ \% = \frac{V - V_{IRA_F}}{V}$$

$$= \frac{\sum_{x=0}^{T}[f(T-x)\sum_{t=x}^{T}\beta^t \cdot E] - \sum_{x=0}^{T}[f(T-x)\sum_{t=x}^{\min T,x+9}\beta^t \cdot (1 - \gamma \cdot \alpha \cdot \Delta I) \cdot E]}{\sum_{x=0}^{T}[f(T-x)\sum_{t=x}^{T}\beta^t E]}$$

$$= \frac{\sum_{x=0}^{T}[f(T-x)\sum_{t=x}^{T}\beta^t] - \sum_{x=0}^{T}[f(T-x)\sum_{t=x}^{\min T,x+9}\beta^t \cdot (1 - \gamma \cdot \alpha \cdot \Delta I)]}{\sum_{x=0}^{T}[f(T-x)\sum_{t=x}^{T}\beta^t]}$$

$$3.4$$

Using a discounting factor of $\beta = 0.9$, when $\alpha = 15\%$ (that is, we estimate each post-approval indication accounts for 15% of the drug's sales), the total revenue will be reduced by 21.5%; while when $\alpha = 25\%$, the total revenue will be reduced by 26.6%. As a result, the decreases in post-approval indications could lead to greater adverse impacts on revenue than if we consider only the direct impact of cutting the key return period in section 3.1, ranging from 21.5% to 26.6% of revenue reduction compared to the previous result of 13.9%. Note that if the estimate is the revenue reduction inside the Medicare market, we then multiply by 30% to be the Medicare drug sales as a percentage of total U.S. sales (KFF, 2019), and arrive at a 6.5% to 8.0% reduction in revenue in the whole U.S. market. In the following discussions, we use the upper bound of 8.0% to estimate the R&D loss associated with the revenue reduction.

Section 3.2 Decrease in R&D Associated with the Revenue Reduction

To arrive at the reduction in R&D investment in the entire U.S. market, we apply the literature on R&D elasticity with respect to revenue to the percentage reduction in revenue found. Utilizing the mean elasticity of 1.54 reported in Philipson and Durie (2021a), which includes a literature review on R&D elasticities, we estimate that R&D will reduce by 6.4% under the direct revenue effect, and by 12.3% under direct and post-approval revenue effects.

We first establish a counterfactual R&D investment for the next 20 years for small molecule drugs following the method in Philipson and Durie (2021a), using the PhRMA membership survey (PhRMA, 2022), and the percentage of small molecule R&D in all IPO fundings reported in Carter et al. (2016). We calculate the compound annual growth rate in global R&D among PhRMA member companies from 2000 to 2021, which yields a growth rate of 6.4%, and apply it to estimate total R&D from 2022 to 2042, whose sum represents the total counterfactual increase in R&D over the next 20 years without the IRA. We multiply this counterfactual R&D by the abovementioned small molecule IPO percentage in Carter et al. (2016) to arrive at the counterfactual R&D for small molecule drugs only.

Then, we approximate the sales share of the top selling small molecule drugs among all small molecule drug sales by calculating their sales share among the top 200 small molecule drugs (J. Chem. Ed., 2021). Though the top 200 drugs cannot represent the entire small molecule market, we note that the 200th drug has an annual sale of less than $0.3 million and the top 200 drugs already have total sales of almost $300 billion, indicating that the rest of the small molecule drugs will hardly impose a significant impact on market sales if neglected. Thus, our approximation should be valid, which suggests that 79.1% of the small molecule drug sales are by the top sellers. Assuming sales share is proportional to the R&D investment share and multiplying the small molecule counterfactual R&D by this 79.1%, we estimate the counterfactual small molecule R&D attributed to the top-selling drugs to be $1.9 trillion for the next 20 years.

With the 6.4% reduction in R&D considering only direct revenue effects of initial indications due to shortening the key return period, this leads to a reduction of $121.4 billion in R&D for the next 20 years.

To benchmark our finding for the implied loss in new drugs, assuming the same proportional loss of 6.4% for a range of 30 to 40 small molecule drugs approved per year, this yields 1.9 to 2.6 fewer new drugs per year for a total of 39 to 52 drugs lost over 20 years. Given that, on average, 32 small molecule drugs have been approved each year in the last ten years (FDA, 2022b), this reduction suggests 41 fewer drugs will be innovated in 20 years. As CEA (2019) indicates, each $2,000 reduction in R&D leads to the loss of 1 life year. We estimate 60.7 million life years to be lost from the reduction in R&D. With the range of VSLY of $100,000 to $490,000, where $100,000 serves as a lower bound and $490,000 comes from the mean value in Philipson and Durie (2021b), a comprehensive literature review on VSLY estimates that the lost life years are valued at $6.1 trillion to $29.7 trillion. At a widely used VSLY of $150,000, the lost life years are valued at $9.1 trillion.

With the 12.3% reduction in R&D considering both the direct revenue effect of initial indications due to shortening the key return period and the additional revenue effects of discouraging post-approval indications, this leads to an even higher reduction of $232.1 billion in R&D investment for the next 20 years. Using the same methodology, this reduction yields 3.7 to 4.9 fewer new drugs per year, with a total reduction of 74 to 98 and an average of 79 small molecule drugs lost through 20 years. Considering all indications, we multiply 79 by 2.4, yielding 188 indications lost. Correspondingly, 116.0 million life years will be lost. Setting the range of VSLY from $100,000 to $490,000, the lost life years are valued at $11.6 trillion to $56.9 trillion, with $17.4 trillion at a VSLY of $150,000.

Section 4: Concluding Remarks

The IRA price setting provisions will harm innovation and in turn adversely affect patient health while reducing drug costs for only select patients. The IRA will shorten the time period manufacturers have to earn returns for small molecule drugs by 40%. In this paper, we estimate the revenue effect of reducing the returns period and discouraging post-approval indications. We find that these revenue losses will lead to 188 fewer small molecule treatments over the next 20 years, including 79 fewer new molecules and 109 post-approval indications. We find that this forgone innovation is expected to lead to 116.0 million life years lost.

Discouraged innovation owing to the IRA would specifically bring obstacles to addressing the medical needs of older Americans. According to PhRMA (2023b), over 400 drugs for chronic diseases commonly seen in older Americans are in development, among which 117 are for Alzheimer's Disease, 20 are for anemia, 53 are for osteoarthritis, 22 are for kidney diseases, 19 are for chronic obstructive pulmonary disorder, 56 are for major depressive disorder, 68 are for diabetes, 20 are for glaucoma and cataracts, and 87 are for heart failures. These drugs have indications including some of the most prevalent diseases in the older population, like Alzheimer's Disease, diabetes, and heart failure. The reduction in innovation would delay or deter cutting-edge solutions to be invented and delivered.

In particular, reduced innovation in small molecule drug development will disproportionately harm certain patient populations, including those seeking advances in treating cancer or central nervous system diseases such as Parkinson's or mental illness for which small molecule drugs can best target the diseases. Additionally, specific attributes of small molecule drugs facilitate more convenient modes of administration and genericization that can improve adherence and grant greater flexibility for patients who face obstacles in accessing care. As such, small molecule drugs can be an important factor in supporting greater adherence and health equity.

Reduced innovation would also harm equality in health as it takes new development and innovation for historically marginalized populations to be taken into consideration. Research shows that the IRA will slow down the growth in overall life expectancy in the U.S. by 9.8% annually and lead to a reduction in longevity convergence between Blacks and Whites by 0.11 years through 2032, which accounts for 10.9% of the projected years of convergence without the IRA (Philipson et al., 2023). Thus, the impact of the IRA on innovation would not only deprive patients of more advanced treatments, but also hinder the path to health equality.

Our analysis of the impact of the IRA's policy to shorten the time to earn a return on investment on small molecule R&D is likely conservative as there are several factors that may operate to yield effects greater than what we assumed but for which credible data sources are lacking. First, the IRA's pricing scheme will likely impact not just the drugs selected for price controls, but also the drugs in the same pharmacologic class that compete with the selected products. Thus, the impact on industry-wide revenues could be significantly larger.

Second, under the IRA, it is possible that the enacted law would delay patient access to new treatments by discouraging launches for limited populations (e.g., R&D development of orphan drugs), and encouraging innovators to wait to launch until they are able to gain broader indications that can take longer to achieve. In addition, the IRA may discourage additional R&D investment into orphan drugs that have already been approved to treat one rare disease. Although orphan drugs with a sole indication are excluded from price negotiation, drugs with multiple orphan designations or indications outside the initial designation (orphan or non-orphan) are not excluded from negotiation. According to the National Organization for Rare Disorders (NORD, 2020), 39.2% of orphan drugs (221 out of 564) have more than one orphan designation or other non-orphan indications.

Third, the IRA could be particularly harmful for cancer innovation that heavily relies on post-approval indications to help patients. For example, cancer drugs usually obtain an initial approval for a particular late-stage cancer and over time, they gain approved uses for earlier stage cancers and combination regimens through post-approval research. Since new indications usually occur several years after the approval of the initial indication, this post-approval R&D would be strongly disincentivized under the price negotiation of the IRA. Specifically, the government-set maximum fair price at 9-years after initial approval is a major disincentive to those indications that would not be approved until years 6 or 7. In some cases, manufacturers factor in the revenue expected to be generated from post approval indications in the decision to develop and launch a new medicine. Therefore, the detrimental effect of the IRA on post-approval R&D for new indications could be an important force to jeopardize small molecule innovation in cancer.

Lastly, no negative pricing effects or spillovers to private markets outside Medicare were assumed. However, such spillovers may be expected for a number of reasons. First, the Maximum Fair Price (MFP) established by the IRA will eventually be reflected in the calculation of Average Sales Price (ASP), a commonly used pricing benchmark for physician-administered drug pricing in the commercial market. Additionally, there is already active legislation in several states to reference the Medicare MFP as a price benchmark in all state-regulated commercial plans. Also, the Maximum Fair Price could reset the Best Price for each state's Medicaid program. Similarly, the mechanism will impact 340 billion prices. After the MFP is published, healthcare payers could use the information as leverage in their plans' negotiations, which would further decrease drug prices in the commercial market.

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