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Policy Brief[1]

The Potentially Larger Than Predicted Impact of the IRA on Small Molecule R&D and Patient Health

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Abstract

This policy brief analyzes the impact of regulatory and legislative changes within the Inflation Reduction Act (IRA) on medical R&D and patient health with respect to small molecule drugs. Initial evidence potentially suggests that the cutbacks in R&D have been larger than predicted by the CBO and we consider three potential explanations: the larger than anticipated effects of a reduced effective patent life, unrecognized class-wide effects of the price-negotiations, and discouraged generic entry.

First, the consequences of the IRA limiting the effective patent life of small molecules through negotiations may be larger than recognized. We find that this cut in effective patent life alone leads to up to 8% reduction in overall industry revenue and a 12.3% reduction in R&D. This reduction in R&D would translate to 79 fewer small molecule drugs or 188 indications, and 116.0 million life years lost over the next 20 years. Many of the small molecule drugs helping vulnerable populations, such as those with HIV or Hepatitis C, would be affected.

Second, the impact of the IRA on class-wide pricing was unrecognized. Not only will prices of negotiated drugs need to be reduced, but competitors are likely to reduce their prices owing to competitive pricing pressure of effective top-sellers being rebated. We find that the share of Medicare spending on small molecule drugs affected by negotiated drugs ranges between be 35% to 86%.

Third, generic entry will be reduced for drugs with large Medicare market shares. We find that 40% of FDA-defined drug classes have over 50% of their sales in Medicare. This market will be especially impacted by the IRA and made less profitable for generics to enter. This is important because reduced generic entry due to IRA Medicare negotiations would raise prices for non-Medicare populations.

We also discuss how the IRA's rules on categories of drugs that are exempt from negotiations distort R&D investments. The policy brief concludes that the overall industry effects of the IRA on small molecule R&D and patient health could be much larger than predicted by the CBO and similar bodies.

Section 1: Introduction

The Inflation Reduction Act (IRA) mandates the negotiation of drug prices covered under Medicare Part B and Part D. The Act will start with ten high-cost, single-source drugs in 2026, rising to 60 drugs by 2029. The Act also requires drug manufacturers to reimburse Medicare if they raise drug prices beyond the rate of consumer inflation.

The announcement of the IRA's implementation appears to have already negatively impacted R&D activities beyond what CBO predicted, with a large number biopharmaceutical firms officially announcing in earnings calls cut-backs or cancellations of drug development programs, citing the IRA in their rationale.

This paper analyzes the potentially larger than anticipated impact of the IRA's regulatory and legislative changes on the medical innovation of small molecules. It explores potential factors driving what appears as a larger than predicted reduction in R&D from IRA through three channels: unanticipated effects of reduced effective patent lives, class-wide effects of negotiations, and the nagtive impact on generic entry. In addition, we discuss how exclusion and exemption rules in the IRA may impact R&D activity. Overall, the policy brief suggests that the IRA will impose heavy burdens on drug manufacturers and discourage their investment in R&D far beyond what the CBO has predicted.

The paper proceeds as follows. Section 2 presents the overview of the IRA negotiations and the evidence on R&D cut-backs obtained from company earnings calls. Section 3 analyses the IRA's impacts through the abovementioned three dimensions. Section 4 discusses the exclusions and exemptions in conjunction with their impacts on R&D. Finally, Section 5 concludes our findings.

Section 2: The Faster Than Predicted Reduction in R&D Activities to Date

2.1 The Content and Uncertainty of the IRA

As mentioned in the introduction, the IRA includes drug price negotiations with manufacturers for lower prices within Medicare, starting with ten high-cost, single-source drugs in 2026, and rising to 60 in total by 2029. In addition, beginning in 2023, drug manufacturers that sell certain products through Parts B and D must reimburse Medicare if they raise drug prices beyond the rate of consumer inflation.

The IRA establishes the Drug Price Negotiation Program for certain drugs covered under Medicare Part B and Part D. Specifically, the Secretary of HHS is responsible for negotiating Maximum Fair Prices (MFPs) with drug manufacturers. The negotiation process will start in 2023 when the Secretary of Health and Human Services publishes a list of their selected highest spending drugs. The negotiation process begins approximately two years before the date that new MFPs take effect each year. Small-molecule drug manufacturers are allowed at least 9 years of effective patent life selling at market-based prices before they must sell their products at or below the CMS-negotiated prices. Because manufacturers would face no incentive to sell below the negotiated prices, we assume they will sell at the negotiated prices throughout our discussion.

During negotiations, the Secretary considers various factors, including drug cost of production and R&D expenditures, federal support, and comparative effectiveness to set the prices below the MFP. The MFP ceiling varies based on the drug type and time in the market,

and it remains in effect until a generic substitute is available. Non-compliant drug manufacturers face penalties in the form of civil monetary penalties or an excise tax, with the amount set as a percentage of the drug's sales price plus the tax imposed by the Act, which could range from 65% to 95% if a manufacturer were out of compliance for more than 270 days. The Act requires drug manufacturers to pay rebates to Medicare if they increase prices.

The negotiation procedure entails much complexity and uncertainty regarding when and which drugs will be negotiated and thus imposes heavy burdens on drug manufacturers. Manufacturers may face huge revenue reductions to fund ongoing R&D if their current drugs are negotiated, and the possibility of being negotiated would urge manufacturers to become extra cautious about where and whether to commit R&D investment.

2.2 The Larger Than Predicted Impact of IRA on R&D Activities to Date

The announcement of the IRA's implementation has already caused negative impacts on R&D activities in the biopharmaceutical industry. Philipson (2023a) discusses evidence from *Horizon Government Affairs* of multiple biopharmaceutical firms that have officially announced the cancellation of drug development programs due in part to the IRA. For example, the drug firm Alnylam announced that its development of a new Stargardt disease treatment would cease due to the IRA. Eli Lilly mentioned that it would stop its development of a blood cancer drug due to the new law (Endpoints News, 2022a). Insmed and Acadia Pharmaceuticals are likely terminating their development for Brensocatib and Prmavanserin, respectively (Horizon Government Affairs, 2022). Additionally, Astra Zeneca's CEO said that the company may have to stop launching certain new cancer drugs because of the IRA reforms (Endpoints News, 2022b). Bristol Myers Squibb expects to defund a few programs for the same reason (Financial Times, 2022). Amgen and Sanofi claimed that the IRA would become a significant barrier that prevents the pharmaceutical industry from creating innovation. Several other major biopharmaceutical firms claimed that a pullback in research would be a choice for the same reason (Biopharma Dive, 2022). Protagonist Therapeutics also terminated the development of Rusfertide due to the IRA.

In addition, a recent survey by PhRMA (2023a) finds that 95% of companies said they expect to develop fewer new indications for existing drugs after the passage of the IRA. Considering a broader scale including R&D, many manufacturers have expressed negative sentiments towards the IRA, as shown by multiple survey reports displayed in Table 1 (Todd Strategy Group, 2022; Horizon Government Affairs, 2022). This evidence suggests that the uncertainty brought by the IRA through drug negotiation procedures can impose heavy burdens on drug manufacturers and discourage their investment in R&D.

Table 1: Company Attitudes Regarding the IRA from Reports

TSG report		
Sentiment	Count	Percentage
Negative Regarding IRA	26	44.8%
Negative Regarding Reforms	4	6.9%
Possibility of Negative Impact	6	1.0%
Neutral but Significant Impact	4	6.9%
Horizon Government Affair		
Negative Regarding IRA	5	45.5%

Notes: "Negative Regarding IRA" is defined by explicit negative terms towards the IRA, e.g. "negative", "challenge", "headwind"; "Negative Regarding Reforms" is defined by explicit negative terms towards general reforms not specific to the IRA; "Possibility of Negative Impact" is defined by the explicit mentioning of possible negative impact, e.g., "may make it difficult"; "Neutral but Significant Impact" is defined by the mentioning of uncertain but significant impact, e.g., "it is likely to be significant".

An analysis of the University of Chicago of a drug-pricing policy similar to the IRA predicted 135 fewer drugs would launch by 2039 (Philipson et al., 2021). To understand the magnitudes found in this study, consider a drug-manufacturer-revenue loss of 15 percent from the IRA, which is similar to both the above analysis and that of the CBO cost estimate (CBO, 2022).A proportional loss in R&D and new drugs would then be close to the University of Chicago's projection. More precisely, a 15 percent cut in the CBO's prediction of 45 new drugs per year would suggest around 6.8 fewer drugs per year, totaling around 121 lost over the 18-year horizon.

The CBO actually projected just five fewer new drug approvals for the same legislation (CBO, 2021) – an assessment that now appears well below observed data as five drugs may have been lost just a few months into the IRA, based on the company calls. Further, these losses only account for existing drugs already under development, not those that will be discarded before early-stage development even begins. Indeed, with at least three reported lost drugs in 4 months, this pace implies 9 per year or 162 in 18 years. If we consider that recent earnings calls indicate that many more than three drugs are in jeopardy, even larger reductions may have occurred.

Section 3: Explaining the Larger Than Predicted Reduction in R&D Activities

In explaining what may be a potentially larger than predicted initial R&D response to the IRA, we consider three factors: effective patent life effects, class-wide pricing effects, and generic entry effects.

3.1 The Larger than Anticipated Cuts in R&D due to Effective Patent Life Losses

According to Phillipson et al. (2023b), the IRA's 9-year benchmark would shorten the effective patent life (EPL) for 82.6% of the 92 blockbusters with sales over $1 billion in 2021. Effective patent life (EPL) is the patent time at a drug's market launch date and calculated as the difference in years between the drug's patent expiration date and its FDA approval date (if multiple patents exist, focus on the strongest patent used for patent restoration). EPL is an important factor that influences R&D investment because it takes many years to recoup the R&D costs and earn a positive return for a new drug introduction (Grabowski et al., 2002). Current U.S. laws state that patent protection lasts for 20 years from when the patent is filed. However, because biopharmaceutical firms spend a large amount of time on product development and regulatory review, the actual remaining patent life at the time of approval is much less and highly variable across drugs. Since the IRA determines that small-molecule drugs approved more than nine years ago would face negotiation, it would shorten the EPL of such small-molecule drugs and thus reduce the revenue of their manufacturers.

Based on Philipson et al. (2023b), the IRA's effective patent life (EPL) cap of 9 years on top-selling small molecule drugs will reduce the expected present value of revenues by 13.9% in the Medicare market, which translates into a lower bound of a 4.2% reduction in revenue from

initial approvals in the entire U.S. market for the next 20 years. Correspondingly, multiplying by an average R&D elasticity of 1.54 (Philipson and Durie, 2021), R&D investment will decrease by 6.4% considering only initial approvals, and up to 12.3% considering both initial and post approvals. As reported in Philipson et al. (2023b), we translate this percentage decrease into effects on small molecule development and life years by constructing a comparative counterfactual. With 32 small molecule drugs being approved each year in the last ten years on average, assuming R&D is proportional to the number of approvals, the 12.3% reduction at the upper bound would lead to 79 drugs or 188 indications not being developed for the next 20 years. To create the counferfactual for life years, we first calculate the compound annual growth rate in global R&D among PhRMA member companies from 2000 to 2021, and apply it to estimate total R&D for the next 20 years without the IRA. We then multiply this counterfactual R&D by a small molecule IPO percentage in Carter et al. (2016) to exclude biologics. Then we approximate the sales share of the blockbuster small molecule drugs in all small molecule sales by calculating the blockbusters' sales share among the top 200 small molecule drugs reported in J. Chem. Ed. (2021), where the drastic differences between the sales of the top 200 small molecules and the sales of the 201st small molecule suggest that the top 200 molecules can approximate the entire market. Obtaining the magnitude of the loss in small molecule R&D from the above approximation, we arrive at the loss over life years using the relation between the $2,000 loss in R&D and one life year lost reported in CEA (2019). In this approach, a 12.3% R&D reduction approximates $232.1 billion in magnitude, leading to 116.0 million life years lost over the next 20 years. Note these estimates are conservative due to the fact that no spillover to private markets outside Medicare and Medicaid Best Price issues are considered.

In addition to the impact on developing new drugs, the reduced EPL would also impact the development of new indications of existing drugs. Because the development of new indications usually takes 6 to 7 years after the approval of the first indication, it can be detrimentally harmed by the effective 9-year EPL. Indeed, developing new indications for existing drugs is one of the major ways that a treatment can advance.

3.2 Unanticipated Class-Wide Innovation Effects

This section assesses the total impact of the IRA on class-wide pricing through competitive pricing effects on non-negotiated small molecule drugs. Even if a drug does not end up under negotiation, if a competing brand in the same class ends up negotiated, large unanticipated price cuts are likely to occur for the drug to compete in the market (Philipson et al., 2023c). As a result, there will also be a reduction in R&D for drugs that compete with negotiated drugs. If the top-spending drugs selected for negotiation are in the top-spending drug classes, then the overall industry effects could be much larger than those assessed by the CBO and similar bodies.

To quantify the overall impact of the IRA on class-wide pricing, we first determine the universe of small molecule drugs. Using data from the FDA National Drug Code Dictionary (2022), we retrieve the list of drugs in all categories, match the information with FDA's Compilation of CDER New Molecular Entity Drug and New Biologic Approvals (2022)[2], and

[2] The dataset provides a listing of all New Molecular Entities (NMEs) approved from 1985 to 2021, including both small molecule drugs approved under a New Drug Application (NDA).

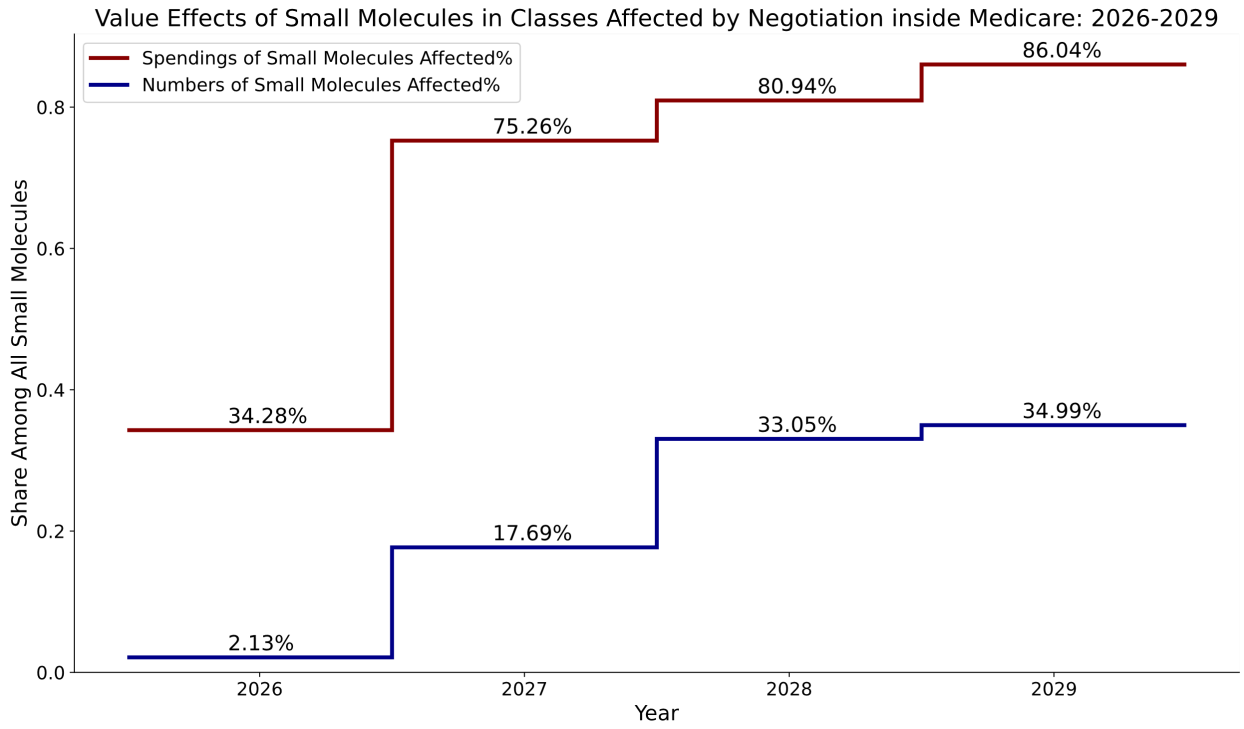
filter the list to the category of small molecules where all small molecules are approved under a New Drug Application (NDA). As a result, we arrive at 2,775 unique small molecules in total.

Second, we estimate the small molecules that are either likely to be negotiated themselves or in a drug class where a drug is potentially negotiated under the IRA through 2029. According to the IRA timeline (CMS, 2022a), drugs without generic equivalents covered under Medicare Part D or Part B that are among the highest-spending Medicare-covered drugs and are nine or more years from FDA approval are eligible for negotiation. Therefore, three main criteria, in addition to criteria like whether the drugs are orphan drugs and whether they face generic competition, are used to check whether these drugs are eligible for negotiation: first, whether they are covered by the Medicare Part B or Part D program; second, whether they have a patent life of more than nine years from their FDA approval date; and third, sorting the drugs that meet the above two requirements in descending order of Medicare spending (CMS, 2022b). According to the IRA timeline released by the CMS (CMS, 2022a), we can estimate the list of 60 drugs for negotiation, that is 10 drugs in Medicare Part D for 2026, 15 drugs in Part D for 2027, 15 drugs in either Part B or Part D for 2028, and 20 drugs in either Part B or Part D for 2029. Among all 60 drugs selected for negotiation, 28 of them are small molecules, as shown in Appendix I. It should be noted that this is only the potential list of drugs being negotiated inferred from our projection using available data, not the definitive list that CMS has yet to release.

Given the predicted list of small molecules selected for negotiation in each year between 2026 to 2029, which is 4 (out of 10), 8 (out of 15), 7 (out of 15) and 9 (out of 20) drugs respectively, and all the other non-negotiated small molecule drugs in the affected pharmacologic classes, we investigate the share of small molecule drugs at risk for negative impacts from the IRA. We consider the total number of small molecules in the same classes as the drugs selected for negotiation each year, using the pharmacologic classes published by the FDA National Drug Code Dictionary (2022)[3]. For example, for the year 2026, the selected 4 small molecule drugs belong to 5 unique classes. Summing all the small molecules from these classes, we arrive at the sum of 59 drugs that will be affected by the negotiation, accounting for 2.1% of the total number of small molecules we considered. Extending the same calculation, we arrive at 491, 917 and 971 drugs affected by negotiation for the years 2027, 2028, and 2029. This includes either small molecule drugs possibly selected for negotiation or in a drug class where a small molecule is potentially negotiated, accounting for 17.7%, 33.1%, and 35% of the small molecules, respectively. We plot our findings depicting the rising share of small molecule drugs affected by the IRA, as shown in Figure 1.

[3] We define drug class as pharmacologic class, using the FDA's "Established Pharmacologic Class" (EPC) methodology.

Figure 1: Share of number and Medicare spending for small molecule drugs that are either negotiated or in a drug class where a small molecule is negotiated



Note: 28 predicted small molecule drugs selected for negotiation: Revlimid (2026), Xarelto (2026), Victoza (2026), Invega (2026), Latuda (2027), Jakafi (2027), Spiriva (2027), Linzess (2027), Xifaxan (2027), Janumet (2027), Genvoya (2027), Farxiga (2028), Tivicay (2028), Lumigan (2028), Incruse Ellipta (2028), Pradaxa (2028), Brilinta (2028), Xeljanz (2028), Venclexta (2029), Atrovent (2029), Uptravi (2029), Otezla (2029), Vraylar (2029), Adempas (2029), Sprycel (2029), Nuplazid (2029), Sandostatin (2029).

The share of Medicare revenue in classes of negotiated drugs is even larger, thereby suggesting that the overall industry effects could be much larger than assessed by the CBO and similar bodies. The Centers for Medicare & Medicaid Services Spending by Drug Database (2022) publishes the annual amount of spending for each covered drug[4]. We find that of the $81.2 billion in annual Medicare small molecule drug expenditures, spending in negotiated classes rises over time from $27.9, $61.1, $65.8, $69.9 billion for the years 2026, 2027, 2028 and 2029. This spending accounts for a respective 34.3%, 75.3%, 81% , and 86% of the annual Medicare-covered small molecule drug spending, as shown in Figure 1. This suggests larger than anticipated industry-wide effects of drug negotiations.

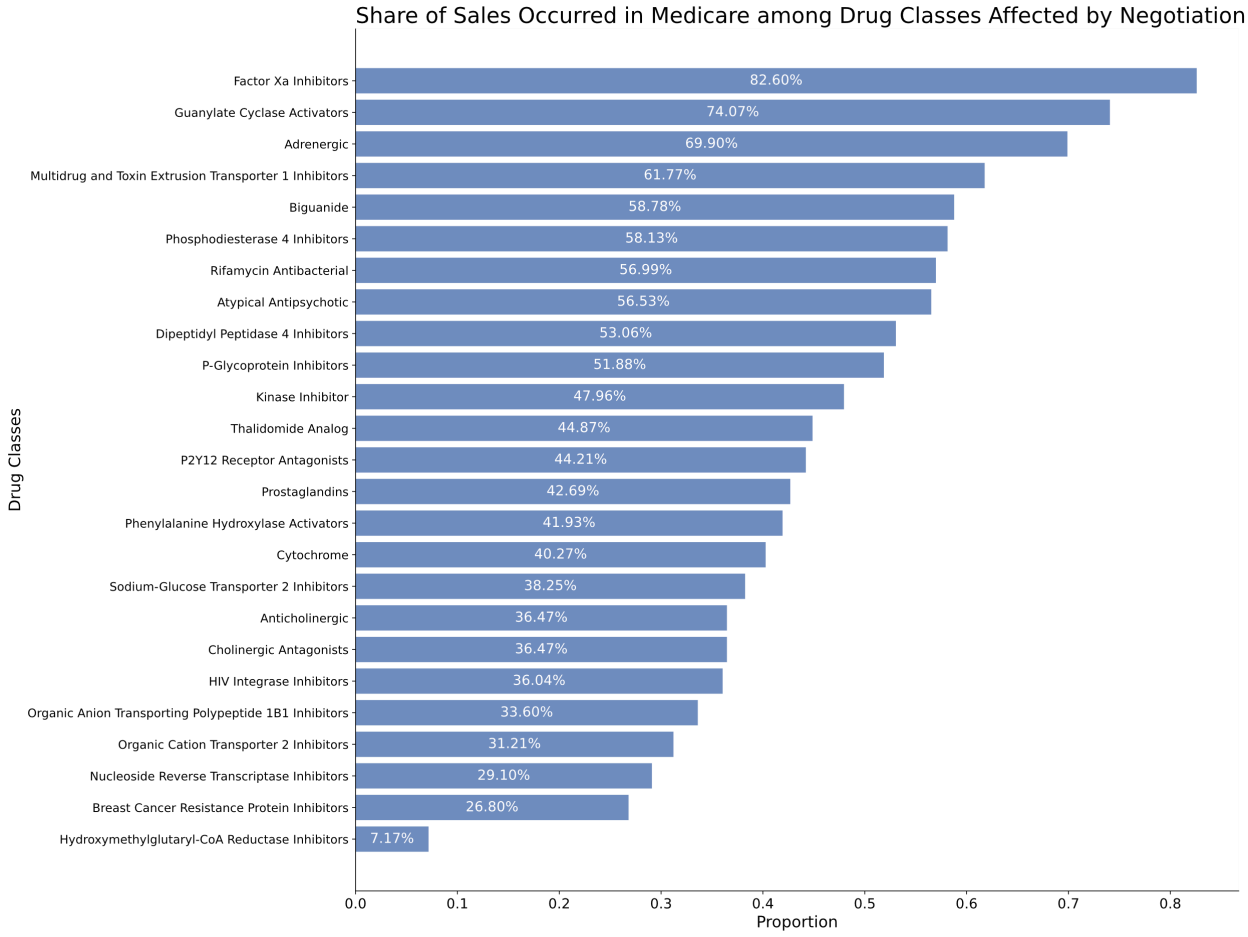
3.3 Impact on Generic Entry

Negotiations applied to drugs with high shares of Medicare sales would lead to particularly detrimental effects for generic manufacturers, who may in turn abandon entry due to lower negotiated prices below sustainable level for entry. This leads to less competition and higher prices for patients not covered by Medicare. If a class is heavily dependent on Medicare sales, such as drug classes to treat oncology or Alzheimer's, the lack of incentives for generics to

[4] The Medicare & Medicaid Spending by Drug datasets provide spending information for drugs in the Medicare Part B (Medical Insurance) and Part D (Prescription Drug Coverage) programs, as well as Medicaid.

enter has adverse consequences outside of Medicare. In addition, there will also be reductions in R&D for generic drug brands that compete with negotiated drugs, as competing brand drugs will need to further lower their prices to remain competitive. To investigate this across drug classes, we examine what share of drug sales or volume occurs in Medicare. The larger the share of sales that occurs in Medicare, the more likely that the overall returns to entry will fall for generics.

Figure 2: The distribution and name of drug classes according to Medicare share of sales



We categorize the 25 drug classes by extracting the unique pharmacologic classes of the 28 small molecule drugs to be negotiated using the FDA's Established Pharmacologic Class (EPC) and Mechanism of Action (MOA), as shown in Appendix II. After specifying the drug classes, we get the total U.S. sales of the small molecule drugs under these classes and calculate the share that occurred in Medicare. We did not access the total U.S. sales of all available drugs but used the five top drugs with the highest Medicare-covered spending in each class. The two main sources to retrieve the total U.S. sales data for each drug used were the financial reports of the manufacturers in FY 2020 and the ClinCalc DrugStats Database (2022). We then calculate the Medicare share of sales by dividing the U.S. total sales by the Medicare spending we already had, as shown in Figure We find that 40% (10 of 35) of the FDA defined drug classes that will likely have a drug subject to negotiation have over 50% of their sales in Medicare. These classes would be most prone to see reduced generic entry that would lead to larger prices outside of Medicare.

Section 4: Exclusions and Exemptions for Negotiation

4.1 IRA Exemption Rules

The IRA has certain criteria for drugs to be eligible for negotiation. Drugs must be FDA-approved for at least seven years and must not be reference-listed products for approved and marketed competitors. However, authorized generics are excluded from the definition of "generic competition". Section 1192(d) also details the small biotech drugs exception until 2029, according to which "Negotiation-eligible drug" precludes drugs for which expenditures for the qualifying single-source drug under part D (or B) is less than or equal to 1%, or greater than or equal to 80% of total expenditure under part D (or B) for all covered part D (or B) drugs in that year. Other exclusions include drugs designated as orphan drugs (i.e. they treat only one rare disease) or drugs or products for which total expenditures under parts B and D are determined to be less than $200 million for the initial price applicability year 2026, adjusted according to the CPI-U for subsequent price applicability years.

One of the exemption rules spares small manufacturers from negotiations. The Inflation Reduction Act has a particular definition for a "specified small manufacturer." Indeed, a specified small manufacturer is a manufacturer of an applicable drug for which in 2021, the manufacturer is a specified manufacturer and "the total expenditures under part D for any one of the specified small manufacturer drugs of the manufacturer that are covered by the agreement or agreements under section 1860D–14A of such manufacturer for such year and covered under this part during such year are equal to or more than 80% of the total expenditures under this part for all specified small manufacturer drugs of the manufacturer that are covered by such agreement or agreements for such year and covered under this part during such year." This definition does have a limitation, though. The IRA states that the term "specified small manufacturer" does not include a manufacturer if they were "acquired after 2021 by another manufacturer that is not a specified small manufacturer, effective at the beginning of the plan year immediately following such acquisition or, in the case of an acquisition before 2025, effective January 1, 2025". Thus, the IRA mandates that specified manufacturers maintain particular expenditure characteristics to be characterized as "small". The small scales of these manufacturers would prohibit these manufacturers to have economies of scale within R&D and production, leading to less efficient innovations.

4.2 Innovation Effects on Orphan Drugs

Specifically, the IRA may discourage further R&D investment into orphan drugs that have already been approved to treat one rare disease. As only orphan drugs with a sole indication, regardless of whether their other indications are approved or not, are excluded from price negotiations, those drugs with multiple indications or with non-orphan indications lack exclusionary permission. According to the National Organization for Rare Disorders (NORD, 2020), 39.2% of orphan drugs (221 out of 564) have more than one designation or other non-orphan indications. However, the IRA brings negative impacts on further R&D into new indications of orphan drugs with its exclusion rules, where private manufacturers may be

discouraged from follow-on orphan drug development (Akin Gump, 2022). This would be contradictory to the Orphan Drug Act, which is meant to encourage the R&D of drugs for rare diseases by providing incentives in the form of regulatory exclusivity.

Based on our previous prediction, we filter the number of orphan drugs likely affected under the IRA using the FDA Search Orphan Drug Designations and Approvals Database (2023). We find that two small molecule orphan drugs (i.e., Revlimid, Jakafi) will be potentially negotiated through 2029 before their exclusively end date. Though it is a small number compared to the 28 total small molecules likely negotiated, since we only consider the orphan drugs that are still in their market exclusivity, the value effects could be more than expected. As reported by the Health and Human Services (HHS) Office of the Inspector General (OIG) (2021), 22 of the 40 drugs in Medicare Part B and Part D with the highest expenditures have been granted at least one orphan designation as of March 2020, among which 12 are approved to treat multiple rare diseases or conditions, and 15 are approved for non-orphan indications as partial orphan drugs. Under drug negotiations, the extended exclusivity of up to seven years available for the orphan drugs may not be as worthy as in the past, as the CMS can price the product at the MFP, much lower than market prices without negotiation, which may greatly reduce the returns to investment and hence discourage R&D development. Additionally, this has a spillover effect to investments in common diseases, as the majority of partial orphan drugs are more likely to be used for non-orphan indications. Evidence shows that only 21% of the total spending on the top-selling partial orphan drugs went to the treatment of rare diseases, while more than 70% went to the treatment of common diseases (Chua et al., 2021).

Section 5: Conclusion

This policy brief analyses the larger than anticipated impact of the IRA's regulatory and legislative changes on medical innovation and patient health, focusing on small molecules.

Specifically, we investigate three different sources of the IRA's impact contributing to the faster than predicted reduction in R&D activities into small molecule drugs. These include reduced effective patent lives, class-wide effects, and deterred generic entry.

First, research finds that the 9-year effective patent life (EPL) of the IRA would cut EPLs for 82.6% of the 92 small molecule blockbusters with sales over $1 billion in 2021. It would reduce the present value of revenues by up to 8% in the U.S. market and cut R&D investment by 12.3% at the upper bound, leading to 79 fewer small molecule drugs being developed, equivalent to 188 indications, and 116.0 million life years lost over the next 20 years.

Second, the class-wide effects of the IRA are larger than anticipated, as non-negotiated drugs can also face price cuts to compete with negotiated ones. Given the predicted 28 small molecules selected for negotiation, we find that by 2029, the potential drugs affected range from 2% to 35% of the total number of small molecules, and they take up 34% to 86% of the total Medicare spending on small molecule drugs, given that top-spending drugs are negotiated. When IRA has effects beyond the drugs negotiated, larger R&D effects than those anticipated or estimated to date will occurr.

Lastly, we find that 40% (10 of 35) of the FDA-defined drug classes that will likely have a drug subject to negotiation have over 50% of their sales in Medicare. This provides a lower incentive for generics to enter, which may reduce the availability of generics and the savings they generate.

In sum, we find that the overall effects of the IRA on small molecule R&D innovation and patient health would be larger than assessed by the CBO and similar bodies. The reduced innovation by the IRA will obstruct older Americans' medical needs by restraining new drug development. According to a report by PhRMA (2023b), more than 400 drugs (primarily for chronic illnesses prevalent in older adults) are currently under development. Among those, 117 are for Alzheimer's disease, 87 for heart failure, 68 for diabetes, 56 for major depressive disorder, 20 for anemia, 53 for osteoarthritis, 22 for kidney diseases, and 19 for chronic obstructive pulmonary disorder. These drugs are intended to treat some of the most common conditions affecting the aging population, such as Alzheimer's disease, diabetes, and heart failure. The decline in innovation would impede the development and delivery of cutting-edge pharmaceutical solutions. Moreover, reduced innovation would deteriorate health equality (ibid), as new developments and innovations are necessary to ameliorate the health concerns of historically marginalized populations. Inevitably, the impact of the IRA on pharmaceutical innovation would not only harm patients demanding advanced treatments, but also place obstacles on the path to health equality.

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Appendix I.

28 Predicted Small Molecule Drugs Selected for Negotiation

1. Revlimid	2. Xarelto	3. Victoza	4. Invega
5. Latuda	6. Jakafi	7. Spiriva	8. Linzess
9. Lipitor	10. Xifaxan	11. Janumet	12. Genvoya
13. Farxiga	14. Tivicay	15. Lumigan	16. Incruse Ellipta
17. Pradaxa	18. Brilinta	19. Xeljanz	20. Venclexta
21. Atrovent	22. Uptravi	23. Otezla	24. Vraylar
25. Adempas	26. Sprycel	27. Nuplazid	28. Sandostatin

Appendix II.

25 drug classes where a small molecule drug is negotiated under the 28 small molecule drugs being negotiated

No.	Pharmacologic Class	Example Usage
1	Adrenergic	Sympathetic Nervous System
2	Anticholinergic	Chronic Obstructive Pulmonary Disorder (COPD)
3	Atypical Antipsychotic	Schizophrenia
4	Biguanide	Type II Diabetes
5	Breast Cancer Resistance Protein Inhibitors	Cancer
6	Cholinergic Antagonists	Chronic Obstructive Pulmonary Disorder (COPD)
7	Cytochrome	Adverse events
8	Dipeptidyl Peptidase 4 Inhibitors	Type II Diabetes
9	Factor Xa Inhibitors	Clotting events
10	Guanylate Cyclase Activators	Constipation
11	HIV Integrase Inhibitors	HIV
12	Hydroxymethylglutaryl-CoA Reductase Inhibitors	Ardiovascular disease
13	Kinase Inhibitor	Cancer
14	Multidrug and Toxin Extrusion Transporter 1 Inhibitors	HIV
15	Nucleoside Reverse Transcriptase Inhibitors	HIV
16	Organic Anion Transporting Polypeptide 1B1 Inhibitors	HIV-1 with advanced immunodeficiency
17	Organic Cation Transporter 2 Inhibitors	Peptic ulcer disease, Indigestion

18	P-Glycoprotein Inhibitors	Angina, Arrhythmia, Hypertension
19	P2Y12 Receptor Antagonists	Acute Coronary Syndromes
20	Phenylalanine Hydroxylase Activators	Myocardial Infarction, Stroke
21	Phosphodiesterase 4 Inhibitors	Chronic Obstructive Pulmonary Disorder (COPD)
22	Prostaglandins	Glaucoma, Gastric ulcer
23	Rifamycin Antibacterial	Traveler's Diarrhea
24	Sodium-Glucose Transporter 2 Inhibitors	Type II Diabetes
25	Thalidomide Analog	Solid tumors, Heart failure

Appendix III.

IRA's Impact on Drug Development

Company	Product	Additional Information
Merck	General pipeline referenced, nothing disease specific mentioned on November earnings call. MRK stated the IRA won't have much of a near-term impact but will have "chilling" longer-term effects	
Alnylam	ALNY discontinuing indication for vitrisiran in Stargardt disease, a rare vision condition.	IRA exempts rare products from price negotiations if each product only treats ONE condition. More than one indication would render it price negotiable. Alnylam's drug is already approved to treat hereditary transthyretin-mediated (hATTR) amyloidosis. Research into the second indication would create a price control and is being discontinued. ALNY_Q3-2022-Earnings_PR_FINAL_10.27.2022.pdf
Eli Lilly	LLY returned a licensed BCL-2 program citing IRA as the reason. "IRA changes many dynamics for small molecules in oncology and when we integrated those changes with this program and its competitive landscape, the program's future investment no longer met our threshold."	Phase I drug was licensed from Fosun Pharma, a BCL2 inhibitor that had been undergoing studies for a variety of blood cancers.
Amgen	Highlighted the IRA as a macro headwind in a recent earnings call	
AstraZeneca	On a November earnings call, AZN said it believes "the IRA has the potential to encourage us to disinvest in small molecules relative to large molecules given the difference in exclusivity, and not launch in the US in smaller indications."	
Sanofi	IRA creates significant uncertainties across the industry, presents a significant challenge to innovation	
Novartis	NVS has said that the key is to differentiate vs. generics, but they do see an opportunity for commercial insurers to obtain more rebates.	

Acadia Pharmaceuticals	We expect ACAD to decline to develop pimavanserin for autism even if its first pediatric Ph2 study reads out positive.	*no action has been taken yet, continue to monitor.
Insmed	Likely to kill its brensocatib Phase2s for rhinitis and HS soon	*no action has been taken yet, continue to monitor.
Neurocrine Biosciences	Because Ingrezza has a surprisingly high ranking on the Medicare spend list, it might face a steep price cut at the end of the decade. ∀ Ingrezza ranked #58 for Medicare spending in 2020 ∀ 12+ higher-ranked drugs will be generic soon ∀ We estimate >50% of Ingrezza sales are to Medicare ∀ If/when tapped for Medicare negotiation, Ingrezza could face one of the steepest imposed discounts. ∀ NBIX has struggled to diversify beyond Ingrezza ∀ The IRA might make NBIX a less attractive M&A target as it would lose "small biotech" cover	Info obtained from 11/13 jeevercoreisi report
BMS	BMS is undergoing a portfolio review due to the IRA. Sounds like oncology will be most affected, and especially small molecules.	Giovanni Caforio, chief executive of the US drugmaker, told the Financial Times it was reviewing its portfolio and expected that some drug candidates would not be funded as a result of reforms in the administration's Inflation Reduction Act. He said cancer treatments would be hardest hit by some measures, which include giving the federal government for the first time the power to negotiate prices for some of the most expensive drugs purchased by Medicare, the taxpayer-funded healthcare scheme for retirees. "I do expect that we will cancel some programmes, whether that is, you know, a full-on indication for an existing medicine or a new medicine. We are undergoing a review of our portfolio now," he said in an interview. "The biggest impact of IRA is actually in oncology. It's in cancer therapy."