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U.S. Pharmaceutical Policy In A Global Marketplace

Reducing copays tends to be a robust and welfare-improving policy, while imposing price controls risks high costs in the hope of a relatively modest benefit.

by Darius N. Lakdawalla, Dana P. Goldman, Pierre-Carl Michaud, Neeraj Sood, Robert Lempert, Ze Cong, Han de Vries, and Italo Gutierrez

ABSTRACT: U.S. consumers generate more pharmaceutical revenue per person than Europeans do. This has led some U.S. policymakers to call for limits on U.S. pharmaceutical spending and prices. Using a microsimulation approach, we analyze the welfare impacts of lowering U.S. prices toward European levels, and how these impacts vary with key modeling assumptions. Under the assumptions most favorable to them, price controls generate modest benefits (a few thousand dollars per person). However, for the remainder of plausible assumptions, price controls generate costs that are an order of magnitude higher. In contrast, publicly financing reductions in consumer prices, without affecting manufacturer prices, delivers benefits in virtually all plausible cases. [*Health Affairs* 28, no. 1 (2009): w138-w150 (published online 16 December 2008; 10.1377/hlthaff.28.1.w138)]

EUROPEANS SPEND LESS THAN TWO-THIRDS as much on biopharmaceuticals per capita as Americans do. Although much of this gap is generated by use of more costly drugs in the United States, rather than pure price differences, there is no doubt that pharmaceutical companies earn more revenue per person in the United States than in Europe.¹ There is growing concern among Americans about whether this spending disparity should persist, or whether new policies should be adopted to limit drug spending.

Pharmaceutical pricing and access involve a trade-off between current and future generations. The prospect of higher future profits creates stronger incentives to innovate, which benefit the future generations who will use tomorrow's inventions. Conversely, policies that ensure high profits typically impose greater spending burdens on patients using today's innovations. As a result, policies that pro-

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mote higher revenues benefit future generations, but possibly at the expense of today's patients. Some critics have questioned the empirical validity of the link between profits and pharmaceutical innovation; however, a great deal of evidence suggests an underlying relationship between the two.²

The second important trade-off in pharmaceutical pricing is global in nature, because new treatments are of value to the entire globe. Thus, spending by Americans encourages innovations that benefit both Europe and the United States. As a result, U.S. spending cuts may harm Europeans.

In this paper we analyze these trade-offs, and we investigate U.S. policy approaches that might overcome them. The heart of this exercise is a global microsimulation model of health and mortality, where morbidity and mortality are affected by baseline health, health behavior, and rates of innovation. We use the model to measure the impact of different policy choices on current and future generations of Americans and Europeans.

Policy Choices

We focused on two general classes of policy interventions: reductions in manufacturers' revenues (holding consumer prices constant), and reductions in the prices paid by consumers (holding manufacturer prices constant). Examples of the former include restrictions on or aggressive negotiation of manufacturer prices. An example of the latter is a subsidy scheme that reduces copayments for consumers, while holding manufacturer prices fixed. We refer to these general classes of policies, respectively, as "price controls," and "copayment reductions."

We considered price control policies that would lower U.S. manufacturers' revenues by 20 percent. We chose this as a benchmark to reflect the findings of our paper on the estimated impact of European price negotiation on revenues.³ We also considered copay reduction policies that would finance 20 percent declines in consumers' out-of-pocket prices, without affecting manufacturer prices. Such policies contrast with price controls; they impose deadweight costs of publicly financing the copay reduction but can boost revenues and utilization.

The copayment reduction policy has acquired particular salience in the wake of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2005, which provided prescription drug insurance to Medicare beneficiaries. MMA specified a "standard benefit" to be offered to beneficiaries through a private-market mechanism. Recent research suggests that the program lowered consumers' out-of-pocket drug spending by just over 18 percent.⁴ Estimated increases in utilization range from 6 percent to 13 percent.⁵ There is some debate about whether Medicare Part D left manufacturer prices unchanged, or whether it lowered them—possibly by as much as 12 percent—by providing market power to private insurers.⁶ If Part D did in fact hold manufacturer prices fixed, it approximates the consumer price reduction we simulate. If not, it represents a hybrid of the two options considered.

Overview Of The Model

We developed a demographic and economic model to predict costs and health status for U.S. and European populations over age fifty-five, based on the Future Elderly Model (FEM) developed for the United States.⁷ The resulting microsimulation tracks over time a U.S. representative sample of people in this age group, and a similar European-representative sample, to project their health conditions, functional status, health spending, and mortality experience. We focused on this age group because of the scarcity of comprehensive health data for younger cohorts. This population accounts for 54 percent of total pharmaceutical spending.⁸ However, the focus on the elderly will tend to understate the importance of future innovation, because the elderly have fewer years to enjoy innovation. More detail about the model is provided in a technical appendix.⁹

■ **Model layout.** The global pharmaceutical policy model (GPM) begins with longitudinal data on respondents age fifty-five and older in the United States and Europe. The longitudinal aspect of the data allowed us to construct probabilities of transition from one health state to another. These transitions were then used to simulate the “aging” of respondents. Health transitions depend on the number of new pharmaceutical products and their likely health effects.

The model includes pharmaceutical policy levers: we allowed for regulation of the price paid to manufacturers and regulation of the price paid by consumers. Lowering manufacturer prices affects the revenues of pharmaceutical firms without affecting consumers’ utilization. Under this scenario, we implicitly held all consumer incentives fixed. In the long run, the model includes feedback between pharmaceutical revenue and the number of new drugs. This may create an indirect effect of price controls on future utilization. The other policy scenario, publicly financing reductions in consumer prices, leads to increased government spending and drug utilization. Moreover, since manufacturer prices do not change, they also lead to higher pharmaceutical revenues, innovation, and drug spending.

■ **Modeling health transitions.** For the United States, we used the Health and Retirement Study (HRS), a nationally representative longitudinal study of the population age fifty and older, collected every two years since 1992. We estimated the rate at which diseases are contracted, as a function of current health conditions, age, and other sociodemographic characteristics (such as sex, race, and risk factors including obesity and smoking). Because of the sparseness of the HRS cohort at age fifty, we used the sample over age fifty-five for all of our modeling exercises. In addition, our baseline scenarios used fifty-five-year-olds to “refresh” the model each period. This held fixed the health and demographic characteristics of our study population and focused attention on the changes in policy and innovation. We modeled the incidence and prevalence of mortality, functional limitation (disability), and the following seven diseases: heart disease, hypertension, diabetes, cancer, lung disease, stroke, and mental illness.

The Survey of Health, Ageing, and Retirement in Europe (SHARE), begun in 2004, is a cross-national database of health, socioeconomic status, and social/family networks for those age fifty and older. Data are available for Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, and Sweden.¹⁰ Simulations for Europe reflect the impact of policy changes on these countries.

The “engine” of the model was a set of hazard functions that simulate aging, mortality, functional limitation, and the occurrence of the seven diseases covered. The incidence of health events was simulated using hazard functions estimated from the data. Using the HRS data, we estimated an individual’s risk of developing a particular condition, as a function of baseline characteristics such as race, smoking status, sex, age, and body weight; all pre-existing diseases; and the individual’s latent propensity toward sickness or health. The latter component allows for the fact that some people are “sicker” or “healthier” than others in unobservable ways.

■ **Incorporating the effects of pharmaceutical breakthroughs.** There are several steps to incorporating the effects of new drug introductions: (1) calculating the rate of innovation, (2) estimating how the rate of innovation responds to policy, (3) assessing the impact of changes in innovation on health transitions, and (4) valuing these impacts. It would be impractical to estimate all health effects for all new molecules, because of limitations on available evidence. Instead, we made the conservative assumption that only the top-selling new drugs improve health. We estimated the probability that a new drug is a top seller and then estimated the average health improvement associated with a top seller. The main steps are as follows.

Step 1: Calculate new drug introductions. We obtained all new drug approvals using the Food and Drug Administration (FDA) “Orange Book” database. We included new chemical entities (NCEs) and reformulation and combination drugs but excluded generics.¹¹ The FDA database maps every approved drug to a therapeutic class. We used consultation with medical experts and structured Web searches to match each therapeutic class to one or more of our seven major disease groups.¹² The result is a list of all new drug introductions, from 1995 to 2002, treating each of our seven diseases.¹³

Step 2: Identify “top-selling” drugs. We estimated revenue in the second year after introduction using data from INGENIX, a large, nationwide, longitudinal claims-based database (1997–2004).¹⁴ This database contains roughly eight million person-years of observations from more than forty employers and detailed information on prescription drug, outpatient, and inpatient spending. INGENIX data on sales of drugs were used to calculate annual revenues in the second year following introduction, for each drug-disease combination. We used insurance claims data—rather than aggregate revenue figures—because we needed to estimate revenues associated with a particular disease.

Step 3: Calculate health effects of drugs. This step is fully described in our appendix.¹⁵ We began with the conservative assumption that only top-selling drugs in each disease category have benefits. We think of new drugs as providing two kinds of

benefits. First, they may improve the health of patients who are using existing therapies that might not be as effective. We estimated these clinical improvements from randomized trial evidence specific to each of our top-selling drugs. We required a published study on the specific drug and the specific clinical pathway—for example, the reduction in the risk that diabetes leads to death, the risk that diabetes leads to hypertension, and so on. Partly as a result of this rigorous standard, our estimated clinical effects (shown in the appendix) were modest.

Second, new drugs may increase the number of people receiving treatment, by reducing side effects or expanding the population eligible for treatment. We used INGENIX data to estimate the impact of “top-seller” launches on the number of patients treated. Newly launched top sellers increased the number of treated patients by about 20 percent within twelve months, as compared to diseases without a newly launched top seller over the same period (see appendix).

When a new drug for disease X is “discovered” in our model, there is some probability that it is a top seller, based on the empirical probability of top sellers in disease X. If it is randomly assigned not to be a top seller, it has no benefit. If it is randomly assigned to be a top seller, it has the clinical and access benefits estimated as described above.

Step 4: Map changes in revenue into effects on innovation. Conceptually, we would like to know how changes in expected future revenues affect today’s research investments and tomorrow’s rate of innovation. The most directly applicable estimate comes from Daron Acemoglu and Joshua Linn, who estimate that a 1 percent change in expected total therapeutic class-level revenue leads to 3–4 percent more annual drugs’ being approved.¹⁶ To our knowledge, no other studies directly estimate the size of this elasticity for the entire market.

The Acemoglu-Linn identification strategy relies on demographic variation. For example, it presumes that increases in the aged population driven by past baby booms or busts increase innovation in drug classes targeted toward the aged.¹⁷ Moreover, they presume that pharmaceutical innovation does not drive these historical trends. This strategy seems plausible on its face, and it recovers the impact of changes in demand on innovation, our effect of interest. Moreover, their estimated effect is quantitatively reasonable. They estimate that a 1 percent increase in market size increases the annual number of drugs discovered by 3–4 percent. More concretely, this translates into innovators producing one additional drug for every additional \$97.5 million of annual potential revenue. Since the cost of an NME is estimated to be \$800 million, this translates into innovators’ demanding a 12 percent annual return on their investment, within accepted boundaries for the return on capital in the pharmaceutical industry.¹⁸

A related study by F.M. Scherer estimates that short-run deviations in gross pharmaceutical profits are approximately proportional to short-run deviations in research and development (R&D) spending.¹⁹ Naturally, short-run deviations in profits have no theoretically justified effect on the long-term payoffs of invest-

ments today. Thus, although interesting, this estimate is less relevant to our model.

Step 5: Map health status and health care use. The HRS and SHARE databases were used to map health status and health care use into spending levels for individuals in the United States and Europe.²⁰

■ **Global effects of policy.** We used the GPM to estimate the global impacts of regulation. We explored three kinds of U.S. policy regimes: price controls, copay reductions, and status quo. We simulated price controls as 20 percent reductions in the revenues earned by manufacturers, holding copayments fixed. We also simulated a 20 percent copay reduction, financed by the government. In the latter scenario, public financing produces deadweight costs of taxation. Estimates of taxes' deadweight costs vary, but a conventional estimate is thirty cents for every dollar of public spending.²¹

To evaluate the welfare implications of each policy, we focused on the key dimensions of health and of medical spending. The net present value of a particular policy is given by the monetized present value of life expectancy, less the present value of medical spending and drug spending.²²

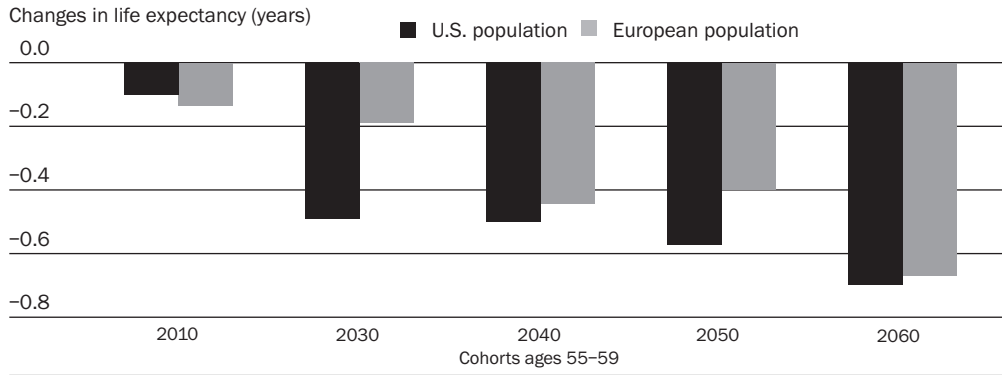
The monetary value of a statistical life-year is controversial. We relied on a middle-of-the-road estimate for our baseline simulations, and varied the number in sensitivity analyses. Richard Hirth and colleagues analyzed forty-two estimates of value of life from the literature and found that in 2004 dollars, the median value of a life-year from revealed preference studies is \$110,200 for studies of nonoccupational safety and \$505,400 for studies of occupational safety.²³ In another influential review of the literature, Kip Viscusi and Joseph Aldy found that the value of a statistical life (rather than life-year) ranges primarily from \$5 million to \$12 million (median: \$7 million).²⁴ Assuming a constant flow of value from life and a real rate of interest equal to 3 percent, these numbers imply values of statistical life-years ranging from \$150,000 to \$360,000.²⁵ As a baseline, we adopted \$200,000 per life-year, but we considered values ranging from \$50,000 to \$300,000.

U.S. Price Controls

Exhibit 1 illustrates the impact of introducing U.S. price controls on the longevity of cohorts ages 55–59, using our baseline parameter values. It shows that the introduction of price controls would reduce life expectancy by two-tenths of a year for Americans ages 55–59 alive in 2010 and by one-tenth for Europeans ages 55–59 alive in the same year. In percentage terms, these correspond to 0.8 percent and 0.7 percent declines from the status quo.

The longevity effects are larger for the older cohorts, because the effects of price controls take time to set in. The early cohorts are not exposed to innovation reductions for a number of years. This dampens the impact on their life expectancy. By 2060, Americans and Europeans in this age group lose almost 0.7 years of life expectancy as a result of U.S. price-control implementation. These represent reductions of approximately 2.8 percent.

EXHIBIT 1
Effect Of U.S. Price Controls On Global Longevity, Among Those Ages 55–59 In The United States And Europe, 2010–2060

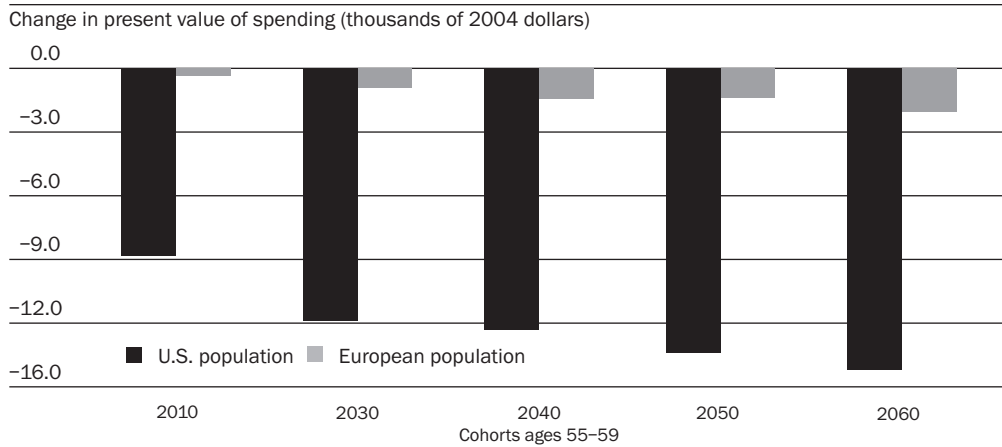


SOURCE: Authors' calculations based on the Global Pharmaceutical Policy Model.

On the benefit side, U.S. price controls reduce spending on drugs and medical care. Exhibit 2 quantifies this effect. Price controls adopted in 2005 would reduce lifetime per capita health spending by \$9,000 in the United States and \$400 in Europe, for those ages 55–59 alive in 2010. Reductions in Europe come about as a result of reductions in life expectancy. The U.S. effects combine life expectancy reductions with direct reductions in cost. For those ages 55–59 alive in 2060, Americans can expect \$14,400 less in lifetime spending; Europeans, \$2,100 less.

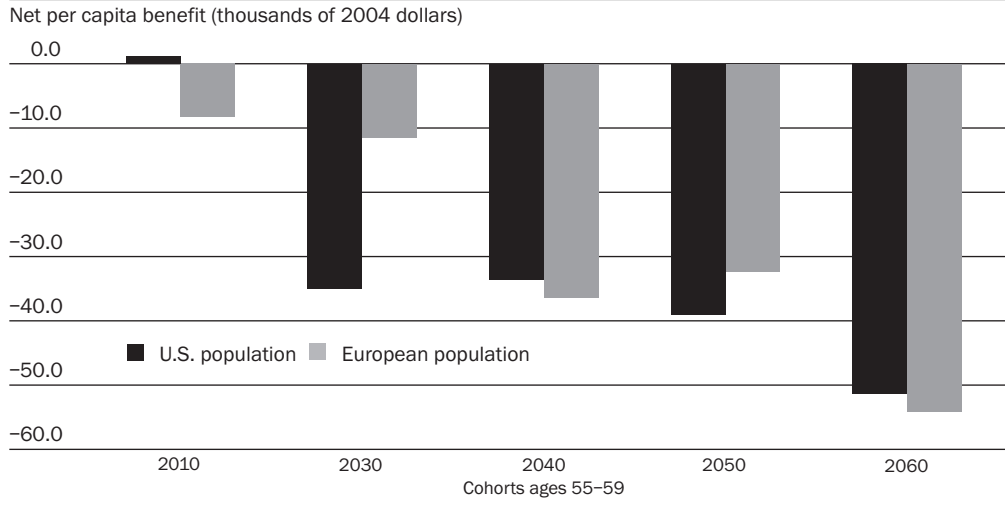
Exhibit 3 shows that U.S. price controls have very modest benefits in the present but substantial costs in the long run. For the 2010 cohort, price controls pro-

EXHIBIT 2
Effect Of U.S. Price Controls On The Present Value Of Lifetime Drug And Health Care Spending, For Cohorts Of People Ages 55–59 In The United States And Europe, 2010–2060



SOURCE: Authors' calculations based on the Global Pharmaceutical Policy Model.

EXHIBIT 3
Net Per Capita Benefit Of U.S. Price Controls To People Ages 55–59 In The United States And Europe, 2010–2060



SOURCE: Authors' calculations based on the Global Pharmaceutical Policy Model.

duce \$1,100 of net per capita benefit in the United States but \$8,000 of net per capita cost to Europeans in that cohort. By 2060, the cohorts ages 55–59 lose \$51,000 and \$54,000 in the United States and Europe, respectively.

U.S. Copayment Reductions

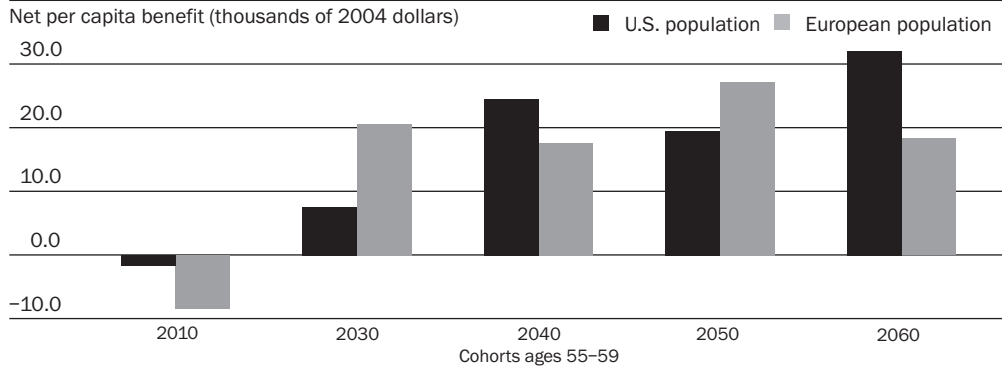
Reductions in consumer prices stimulate innovation by increasing the use of drugs, and thus raising revenue; they raise drug spending for the same reason. For a similar-size reduction in U.S. consumer copays, the 2060 cohorts in the United States and Europe can expect to gain about 0.5 and 0.2 years of life, respectively.²⁶ These are somewhat smaller than the reductions caused by adoption of price controls. Lifetime medical and drug spending for these cohorts goes up by \$7,900 in the United States and \$1,200 in Europe.

Exhibit 4 reports the net value of the copay reduction policy, in terms of per capita benefit to cohorts of people ages 55–59. The earliest cohorts of people ages 55–59 experience declines in welfare, equal to just \$1,700 per American and a still modest \$8,400 per European. The later cohorts experience larger benefits, equaling \$32,100 per American and \$18,300 per European in the 2060 cohort. Copay reductions stimulate increases in revenues and ultimately in innovation, which generates substantial long-run benefits.

Robustness Of Policy Recommendations

The baseline structure of the model implies that copay reduction policies benefit both current and future generations, while price controls do the opposite. It re-

EXHIBIT 4
Net Per Capita Benefit Of U.S. Copay Reductions To People Ages 55–59 In The United States And Europe, 2010–2060



SOURCE: Authors' calculations based on the Global Pharmaceutical Policy Model.

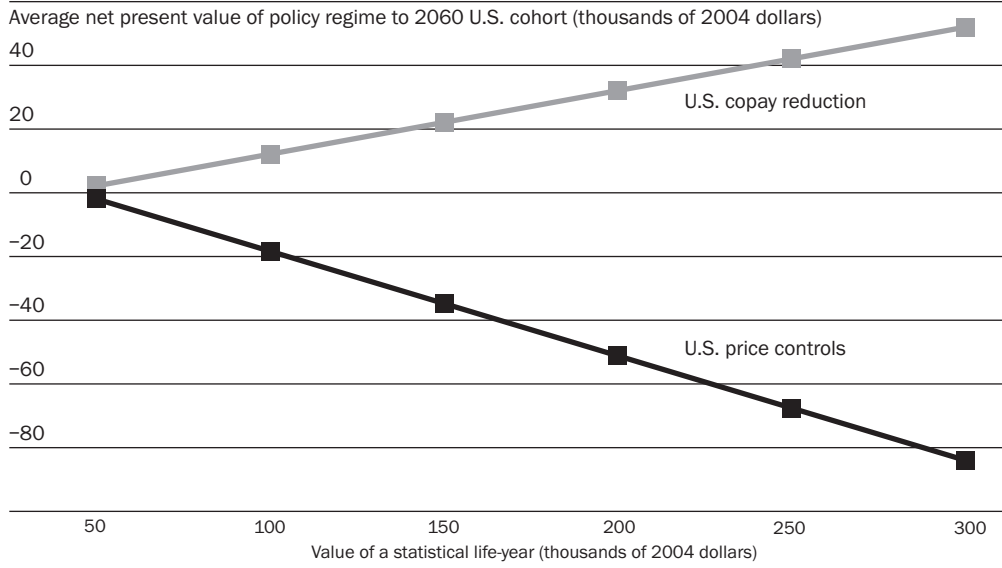
mains to show that these results are robust to the inevitable uncertainty surrounding our parameters. Our quantitative analysis and testing of the model revealed that the estimated value of policies varied with respect to three key parameters: the value of a statistical life-year; the value of new drug introductions; and the responsiveness of innovation to changes in revenue. For all other parameters, our estimates proved insensitive.

Exhibit 5 shows how the value of a statistical life-year affects the U.S. per capita net present value (to the 2060 cohort of those ages 55–59) of both policy interventions, relative to the status quo.²⁷ The qualitative predictions of the model—regarding which policies are beneficial and which are costly—do not depend on the value of a life-year (\$50,000–\$300,000). However, higher values of life translate into larger costs for price controls, and greater benefits for copay reduction, because the value of stimulating innovation is positively related to the value of life.

The next parameter of quantitative importance is the probability of being a top seller. These were estimated empirically for each disease category. To assess sensitivity, we varied the estimate across its 95 percent confidence interval (CI).²⁸ Reducing the probability of being a top seller—that is, a drug that has any benefit—makes price controls less costly and copay reductions less beneficial. Near the bottom of our confidence intervals, price controls generate \$4,200 of total benefit per person. At the mean value, they generate costs just over \$51,000.

The final parameter of quantitative relevance is the responsiveness of innovation to revenues. Estimates in the economics literature suggest that a 1 percent increase in pharmaceutical revenues leads to more than a 3 percent increase in the number of new molecules.²⁹ We considered values ranging from zero to 5 percent. Because several papers in the literature suggest that innovators respond to revenues, zero seems a strict lower bound.³⁰ Exhibit 6 plots the impact of changes in this parameter on the net present value of policy to cohorts of people ages 55–59.

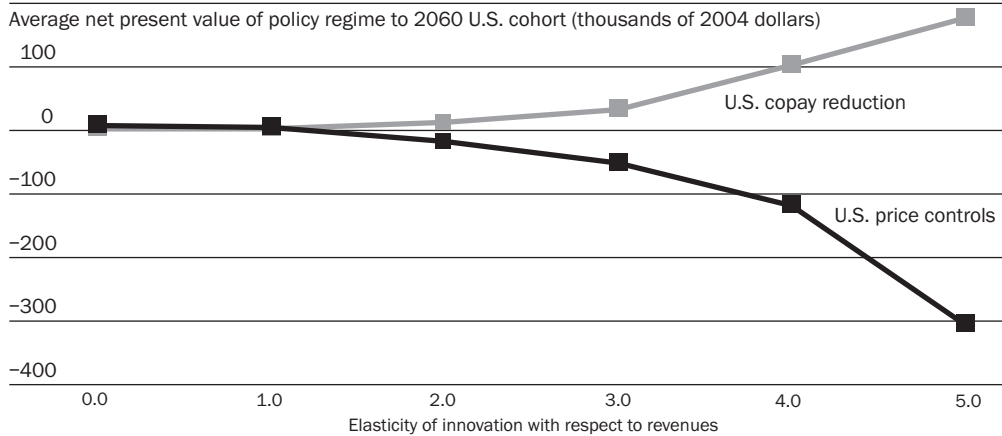
EXHIBIT 5
Value Of A Statistical Life-Year And Implications For The Model



SOURCE: Authors' calculations based on the Global Pharmaceutical Policy Model.

When innovation does not respond to revenue at all, U.S. price controls generate \$8,000 of benefit per person to the 2060 cohort of people ages 55–59 or impose up to \$109,000 of cost. At or below a value of 1.0, price controls become beneficial. The key drawback of price controls is not their obvious costs or benefits, but instead their risk. On the other hand, copay reductions remain beneficial throughout, except for a very small cost when innovation does not respond to revenues at all—a relationship that has been repeatedly rejected in the empirical literature.

EXHIBIT 6
Responsiveness Of Innovation To Revenue And Implications For The Model



SOURCE: Authors' calculations based on the Global Pharmaceutical Policy Model.

Discussion

When innovation responsiveness is relatively low or beneficial drugs relatively scarce, U.S. price controls may create small but positive benefits for consumers. When these parameters are at or above plausibly estimated values, however, the same policies are extremely costly for consumers. As such, price controls represent a risky policy strategy that may have either modest pay-offs or large costs, depending on the responsiveness of innovation. On the other hand, copay reductions overcome the intrinsic trade-offs associated with drug pricing by making both current and future generations better off and by benefiting consumers at home and abroad. They do so by encouraging utilization at the same time that they stimulate innovation. Thus, copay reductions represent the more broadly beneficial choice for U.S. policymakers.

Although the model is complex, its results are driven to some extent by simple arithmetic. Even at highly conservative valuations, life is the most expensive good in the model—more than drugs or other health care. Therefore, cost containment policies that have even fairly modest impacts on longevity will tend to be harmful, while “expensive” policies that produce modest life extensions will be beneficial.

For our baseline parameter values, price controls cost more than \$50,000 per person in the latest cohorts studied, while copay reductions add about \$30,000 of value per person in the same cohorts. In the context of policy changes, these are quite significant values—on the order of the changes induced by the introduction of Medicare.³¹ Viewed in terms of longevity, rather than dollars, baseline scenarios imply that price controls reduce U.S. and European longevity by 0.7 years, equivalent to 2.8 percent and 2.3 percent, respectively.

These are fairly significant gains in longevity compared to major medical breakthroughs such as the advent of revascularization surgery for heart patients. The latter is estimated to have increased longevity by 1.1 years for the treated population.³² Although the lifetime risk of revascularization surgery for those ages 55–59 is not readily available, we can construct an upper bound by noting that the lifetime risk of cardiovascular disease is 62–67 percent for males of that age group and 57–59 percent for females.³³ Employing the conservative assumptions that everyone diagnosed with heart disease gets revascularized and that everyone responds as well to the surgery as those who actually get it, this would imply that revascularization added about 0.6 years of life to the population, on average. Moreover, although our extrapolation method tried to be conservative, some researchers have argued that the 1.1-year benefit is an overestimate, so that the average effect of revascularization may be well below 0.6 years.³⁴ Further context for our longevity estimates comes from research on the longevity impacts of new drug launches. Frank Lichtenberg estimates that from 1986 to 2000, life expectancy increased by 0.8 years because of NCE launches, or by 0.056 years annually.³⁵

Implementing price controls in the United States would have adverse effects on

European consumers, by depressing rates of innovation. These global linkages create major policy problems in an international marketplace, because a given country does not fully realize the benefits (or costs) of its own policies. European price controls, for example, have smaller effects on innovation, because of the presence of a large U.S. market, which acts as a counterweight to policies that reduce European revenues. Moreover, some of the costs that do accrue end up being borne by U.S. consumers, further dampening Europe's incentives for higher prices.

Any single scenario may be incorrect, since many of the needed parameters are difficult to estimate. Our more general finding is that from a long-run global perspective, reducing copayments tends to be a robust and welfare-improving policy, while imposing price controls risks large costs in the hope of a relatively modest benefit. Policymakers facing uncertainty about the structure of pharmaceutical markets may find copay reduction to be a safer strategy than price controls, and one that is extremely likely to improve welfare over the status quo.

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NOTES

1. P.M. Danzon and M.F. Furukawa, "Prices and Availability of Biopharmaceuticals: An International Comparison," *Health Affairs* 25, no. 5 (2006): 1353-1362.
2. A. Finkelstein, "Static and Dynamic Effects of Health Policy: Evidence from the Vaccine Industry," *Quarterly Journal of Economics* 119, no. 2 (2004): 527-564; W. Yin, "Three Essays on the Economics of Health and Development" (Ph.D. thesis, Princeton University, 2005); and P.M. Danzon, Y.R. Wang, and L. Wang, "The Impact of Price Regulation on the Launch Delay of New Drugs—Evidence from Twenty-five Major Markets in the 1990s," *Health Economics* 14, no. 3 (2005): 269-292.
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4. F.R. Lichtenberg and S.X. Sun, "The Impact of Medicare Part D on Prescription Drug Use by the Elderly," *Health Affairs* 26, no. 6 (2007): 1735-1744.
5. *Ibid.*; and W. Yin et al., "The Effect of the Medicare Part D Prescription Benefit on Drug Utilization and Expenditures," *Annals of Internal Medicine* 148, no. 3 (2008): 169-177.
6. M. Duggan and F. Scott Morton, "The Effect of Medicare Part D on Pharmaceutical Prices and Utilization," NBER Working Paper no. 13917 (Cambridge, Mass.: National Bureau of Economic Research, 2008); and Lichtenberg and Sun, "The Impact of Medicare Part D."
7. D.P. Goldman et al., "Consequences of Health Trends and Medical Innovation for the Future Elderly," *Health Affairs* 24 (2005): w5-r5-w5-r17; and D. Goldman et al., *Health Status and Medical Treatment of the Future Elderly: Final Report* (Santa Monica, Calif.: RAND, 2004), TR-169.
8. This figure is based on the authors' calculation using data from the 2005 Medical Expenditure Panel Survey (MEPS).
9. The Technical Appendix is online at <http://content.healthaffairs.org/cgi/content/full/hlthaff.28.1.w138/DC2>.

10. The United Kingdom is not included in SHARE.
11. This excludes vaccines and biologics.
12. Because of the time range of the INGENIX data set, the list was limited to drugs approved by the FDA from 1995 to 2002. Using alternative time frames increased the estimated value of innovation.
13. We were interested in ranking drugs by total lifetime sales, but this was unobserved. Fortunately, as shown in Technical Appendix C (Note 9), the pairwise correlations between ranks calculated using the first, second, third, or fourth full year after launch are typically above 0.9, and often above 0.95.
14. We deflated expenditures using the overall Consumer Price Index (CPI).
15. See the online Technical Appendix, as in Note 9.
16. D. Acemoglu and J. Linn, "Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry," *Quarterly Journal of Economics* 119, no. 3 (2004): 1049–1090.
17. They show that their results are largely unchanged if they focus entirely upon demographic changes resulting from fertility trends, rather than mortality trends.
18. For the cost of an NME, see J.A. DiMasi, R.W. Hansen, and H.G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (2003): 151–185. Aswath Damodaran estimates the cost of capital in the pharmaceutical industry to be just under 12 percent. See A. Damodaran, "Return on Capital (ROC), Return on Invested Capital (ROIC) and Return on Equity (ROE): Measurements and Implications," New York University Working Paper (New York: New York University, July 2007). Since Acemoglu and Linn include new formulations as well as NMEs, the average cost of development might be lower than \$800 million and the estimated return higher.
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20. Exchange-rate fluctuations during 2000–2007 had only a 5–7 percent effect on our cost estimates.
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