Pharmaceutical Innovation and Public Health

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I. Introduction

In this chapter, I explore the gains and costs that follow from pharmaceutical innovation along with their prospective effects on public health. I also review the regulatory interventions that have impacted current outcomes. Improvements in public health are greatly improved by the introduction of new pharmaceuticals. However, those advances are extraordinarily expensive to discover, test, and introduce. How these costs are paid is therefore an essential matter for public health.

There is a wide range of conflicting positions on how the innovative process should be structured and financed. At the center of this debate is the need to balance the dynamic gains from innovative drugs against the static benefits that flow from low drug prices. A critical issue is the extent to which the prices charged for new pharmaceuticals reflect the health benefits provided.

In the pages to follow, I explore such matters along with the major policy actions that have been taken. In large measure, the current structure of pharmaceutical supply and innovation results from the regulatory interventions that have been made. Following a review of the available evidence, I offer both economic evaluations and suggestions for policy adjustments.

II. Critical Role Played by Patent Protection

Among the most long-standing public actions affecting pharmaceutical Innovation are those intended to protect the rights of inventors and developers to their own discoveries. Interestingly, that objective is specifically included among the congressional powers recognized in the U.S. Constitution: As stated there, Congress is specifically authorized “to promote the

Progress of Science and useful arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."[1].

U.S. patent laws are also founded on established economic principles. Creating the information leading to innovative drugs is a classic example of a public good. Such goods are defined as those that "once produced, no one can be excluded from benefiting from its availability."[2] Without governmentally imposed excludability, investments in information generating efforts would be far more limited Effective government programs ae thus an essential feature needed to promote industry research and development efforts. In this setting, pharmaceutical R&D spending is invariably impacted by policies employed to prevent unauthorized usage for specified periods of time.

While proposals are sometimes made to reward innovators according to the social benefits provided by a new pharmaceutical[3], that approach necessarily requires public agencies to determine their social benefits from little market data. Invariably, the proposed rewards would need be compatible with governmental budgetary concerns. And where innovative returns are understated, innovative efforts are diminished.

Applied to pharmaceuticals, there are proposals that drug prices be determined through government controls according to their presumed cost effectiveness.[4] However, as reported below, that approach when adopted has led to much reduced support for pharmaceutical innovation relative to that resulting from the market system actually employed in the United States.

III. Health Benefits from Pharmaceutical Innovation

Few patients directly enjoy swallowing a tablet or accepting an injection. However, they benefit from the improved health that follows from ingesting a drug. The demand for pharmaceuticals thereby rests on the prospective therapeutic benefits that result from taking it. These benefits are commonly measured by two indices: first by a drug's impact on longevity, as

[1] U.S. CONST. art. I, § 8.

[2] Walter Nicholson & Christopher Snyder, MICROECONOMIC THEORY: BASIC PRINCIPLES AND EXTENSIONS 696 (12th ed. 2016).

[3] Peter J. Neumann, Joshua T. Cohen & Daniel A. Ollendorf, THE RIGHT PRICE: A VALUE-BASED PRESCRIPTION FOR DRUG COSTS (2021).

[4] William S. Comanor et al., *Value Based Pricing of Pharmaceuticals in the US and UK: Does Centralized Cost Effectiveness Analysis Matter?*, 52 REV IND ORGAN 502 (2018).

commonly measured by data on life expectancies; and second by the estimated Quality Adjusted Life Years (QALYs) gained. The first index is a population measure and refers typically to a country or community while the second describes the benefits gained by individual patients from specific pharmaceuticals.

Consider first the lengthy study by Frech and Miller of the productivity of pharmaceuticals across OECD countries.[5] Their research estimated the determinants of male and female life expectancies at birth and also at ages 40 and 60. They find that pharmaceutical consumption has little effect at birth but much greater effects on life at ages 40 and 60. Indeed, they conclude that "doubling pharmaceutical expenditures would increase life expectancy at 40 by roughly 2% and life expectancy at 60 by about 4%."[6]. In contrast, they observed that expenditures on non-pharmaceutical health care has had a minimal impact on life expectancies among OECD countries.

In a companion study[7], they employed more recent data specifically to distinguish effects of pharmaceutical consumption from that of non-pharmaceutical medical care. Consistent with their earlier findings, they reported that the latter "did not have a statistically significant effect on life expectancies" in contrast to the significant effects they had found for pharmaceutical therapies.[8]

In a related study, Lichtenberg studied the effects of drug introductions in 52 countries.[9] He employed UN data on life expectancies at birth which increased on average from 46.5 years in 1950-55 to 65.0 years by 1995-2000. Interestingly, potential life expectancies had increased most rapidly in less-developed regions. When these data were grouped according to disease category, country and year, he concluded that "NCE (new chemical entities) launches … account for a significant fraction of the increase in longevity in the sample as a whole" and also that "launch delays reduce longevity".[10]

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[5] H.E. Frech III & Richard D. Miller Jr., THE PRODUCTIVITY OF HEALTH CARE AND PHARMACEUTICALS: AN INTERNATIONAL COMPARISON (1999).

[6] *Id.* at 46.

[7] Richard D. Miller Jr. & H.E. Frech III, HEALTH CARE MATTERS: PHARMACEUTICALS, OBESITY, AND THE QUALITY OF LIFE (2004).

[8] *Id.* at 39-40.

[9] Frank R. Lichtenberg, *Pharmaceutical Knowledge-Capital Accumulation and Longevity, in* MEASURING CAPITAL IN THE NEW ECONOMY 237-74 (Carol Corrado et al. eds., UNIV. CHICAGO PRESS, 2005).

[10] *Id.* at 264.

A more recent study accounts for the major increase in U.S. life expectancy of 3.3 years in the 25-year period between 1990 and 2015.[11] The authors reviewed available evidence on both societal changes as well as the policy actions taken during those years. They reported that of the 12 factors that apparently had the greatest impact, the two leading factors were Public Health Measures and Pharmaceuticals: 44% of the longevity advance was attributable to the Public Health Measures while 35% was attributable to Pharmaceuticals, but only 13% to "Other Medical Care."[12] The pharmaceutical benefit attributions were made after accounting for the opioid catastrophe that occurred during those years.

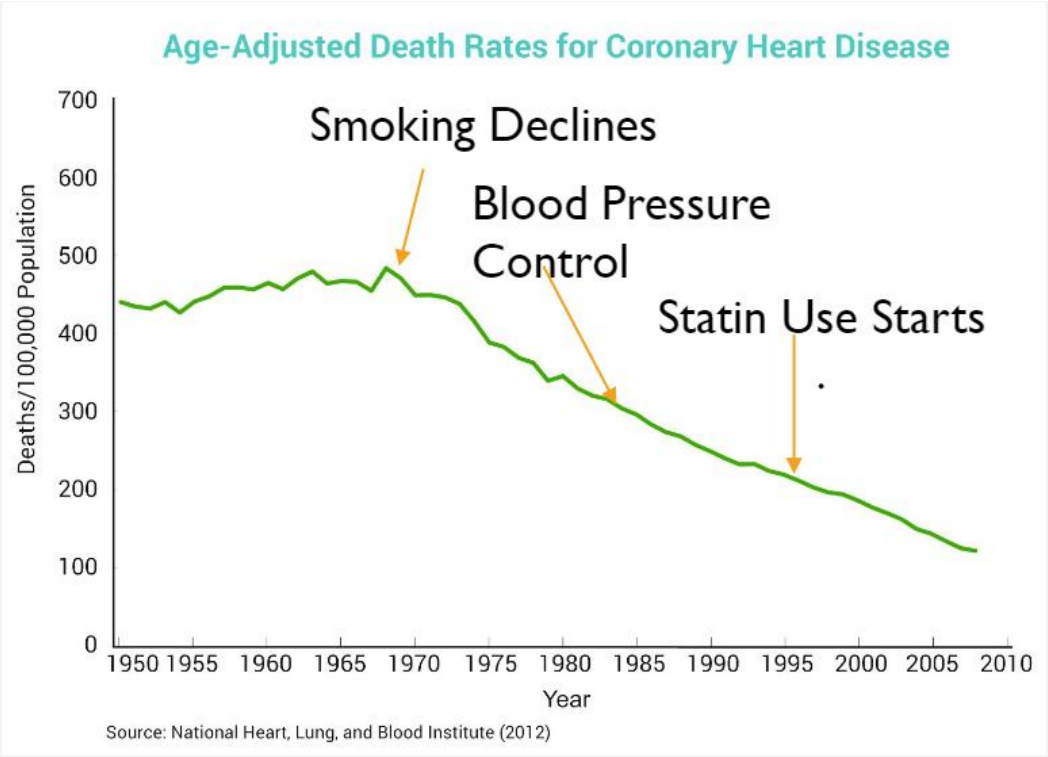
Among the most significant class of pharmaceuticals leading to improved health outcomes are the Statins employed to reduce serum cholesterol associated with heart disease. Indeed, there is evidence that statin use has reduced the prospect of "serious cardiac events."[13] Since the latter 1960s, there has been a substantial decline in CHD deaths for which Statin use has contributed. To be sure, other factors such as smoking decline and improvements in cardiac care may also have played an important role. See Figure 1 for relevant evidence.

[11] Jason D. Buxbaum et al., *Contributions of Public Health, Pharmaceuticals, and Other Medical Care to US Life Expectancy Changes, 1990-2015*, 39 HEALTH AFFAIRS 1546-56 (2020).

[12] *Id.* at 1553.

[13] Robert Kaestner, Michael Darden & Darius Lakdawalla, *Are Investments in Disease Prevention Complements? the Case of Statins and Health Behaviors*, 36 J HEALTH ECON. 151-63 (2014).

Figure 1
Correlates of the Decline in CHD Deaths



While the studies noted above emphasize generalized gains in life expectancies, there is also related evidence from the two major epidemics that recently afflicted the United States. The AIDS epidemic appeared in the late 1970s and reached a peak incidence in 1993-94 of 160,000 cases annually. By 2005, there were more than 900,000 diagnosed cases and 500,000 AIDS related deaths.[14]

That epidemic triggered major R&D efforts leading to the introduction of Protease Inhibitors which were followed by a series of improved medications. As a result, life expectancy, conditional on an AIDS diagnosis increased from an estimated 2.9 years in 1995 to 9.5 years in 1994, and then by 16.5 years by 2000.[15]

The authors estimated aggregate variable costs of production of the drugs involved at $11.1 billion and aggregate firm net revenues at $62.9 billion. In contrast, the total estimated value of

[14] Tomas J. Philipson & Anupam B. Jena, *Who Benefits from New Medical Technologies? Estimates of Consumer and Producer Surpluses for HIV/AIDS Drugs*, 9 Forum for Health Econ. & Policy 1-33 tbl.2 (2006).

[15] *Id.* at §2.3 & tbl.2.

survival gains from 1980 through 2000 even when a minimally assumed value of $100,000 per QALY when discounted to 1980 is nearly $400 billion while ignoring future gains from these therapies. In that case, company revenues would represent only 15% of the medications' total value. This percentage would be lower if future benefits were also included.[16]

A more recent epidemic led to a similar pharmaceutical response, although this time in the form of the development of effective vaccines. So severe was this pandemic that an estimated 8.2 million people died world-wide as a result.[17] However, a recent study estimated a 26% reduction in Covid 19 deaths when compared with the earlier absence of vaccination campaigns.[18] The authors concluded: "The Covid 19 vaccination campaigns across 141 countries averted 2.4 million deaths by August 2021".[19]

While these studies provide evidence of the generalized societal benefits derived from pharmaceutical innovation, they do not deal with the gains resulting from individual drugs. Such gains are not reflected in macro data on life-years gained or deaths prevented but instead by the QALYs gained from specific drugs. Available evidence on the connection between product prices and QALYs gained is presented below.

IV. The Costs and Benefits of Innovation

Costs and benefits from new pharmaceuticals are related conceptually through production functions that represent connections between R&D investments and the introduction of innovative drugs. See Comanor (1965) for an early estimate of this function.[20] That study explored the impact of R&D efforts on pharmaceutical innovation, as measured by new drug introductions multiplied by their sales in the first two years following introduction. In this manner, the relative importance of each new pharmaceutical is acknowledged. The resulting estimated equations are strongly positive and curvilinear in form suggesting that returns increase as R&D efforts expand. In

[16] *Id.*

[17] Covid Mortality Collaborators, *Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21*, 399 THE LANCET 1513-36 (2022).

[18] Virat Agrawal et al., *The Impact of the Global COVID-19 Vaccination Campaign on All-Cause Mortality*, USC Price School of Public Policy, 2024.

[19] *Id.* at 22.

[20] William S. Comanor, *Research and Technical Change in the Pharmaceutical Industry*, XLVII REVIEW OF ECONOMICS AND STATISTICS 182-90 (1965).

addition, firm size is a separate relevant factor. While economies of scale in R&D appear with smaller firms, they disappear in larger firms.[21]

The supply of innovative drugs depends on the pace of underlying R&D efforts. However, there is a wide range of estimates of capitalized pre-launch R&D costs. Detailed estimates range from a low of $161 million to a high of $4.54 billion in 2019 U.S. dollars.[22] With this wide range of values, it has been suggested that "there is no universally correct answer regarding the how much it costs, on average, to research and develop an NME (new molecular entity)".[23] In effect, aggregate costs depend critically on the economic objectives pursued.

Fundamentally, the pharmaceutical sector includes a heterogeneous set of companies. Some firms invest in more risky projects with major therapeutic advances possible even when unlikely, while others are more risk adverse and invest smaller amounts with more assured outcomes. Another source of heterogeneity is the extent to which some companies rely more heavily on university/government research findings while others engage more directly in basic scientific research themselves. R&D costs per new pharmaceutical should be much greater in the latter case than the former. What these observations suggest is that R&D costs per new pharmaceutical can differ substantially across both projects and companies.

The two most prominent estimates are those by DiMasi[24] and Wouters.[25] The former's most recent estimate is $2.6 billion of capitalized costs per approved new pharmaceutical in 2013 dollars, corresponding to $2.8 billion in 2018 dollars. In contrast, Wouter's estimate is less than half that figure at $1.3 billion in 2018 dollars. Such differences turn on the very different samples employed in the two studies. While DiMasi's sample was limited to 10 large pharmaceutical companies that introduced 106 new drugs, Wouter's study rested on 47 different companies that together introduced 63 new therapeutic agents. As acknowledged by the author, the latter group included smaller firms with "leaner operations than larger ones."[26]

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[21] *Id.* at 184-8.

[22] Michael Schlander et al., *How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment*, 39 PHARMACOECONOMICS 1243-69, 1243 (2021).

[23] *Id.*

[24] Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J HEALTH ECON 20-33 (2016).

[25] Olivier J. Wouters, PhD et al., *Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018*, 323 JAMA 844-53 (2020).

[26] *Id.* at 852.

Wouter's study included a larger proportion of Orphan Drugs with lower sales volumes.[27] Firms are less likely to invest large sums for prospective drugs that have more limited markets. To be sure, such products can still have substantial prospective returns due both to the higher prices that are sometimes charged as well as greater prospects for longer periods of exclusivity. Including all these various factors, the costs of innovation are more likely represented by DiMasi's larger cost figurer than Wouter's smaller one.

The widely different results from the two surveys suggest the judgment that innovative efforts more likely require pursuing more uncertain paths than those found with more conventional objectives. Companies that emphasize developing "me too" products, designed to compete with established drugs, are less likely to pursue riskier research programs. Instead, they are more likely to follow well-trodden paths.

While the aggregate costs of pharmaceutical innovation are important, one needs also to consider the types of activities that together comprise total R&D costs. See Table 1 for the various cost categories that comprise these outlays. As indicated there, basic, non-clinical efforts absorb less than one-fifth of the total. In contrast, the various phases of clinical trials, as required by the Food and Drug Administration, total just under 60% of the total. Note that three sets of clinical trials are required in New Drug Applications, while a fourth set is carried out following drug approval. At each stage, a prospective pharmaceutical faces substantial risk of failure. See Figure 2 for the reported transition probabilities along with the overall probability of success. Not only is pharmaceutical research and development a highly expensive enterprise, it is also a highly risky one.

[27] *Id*. at 851-2.

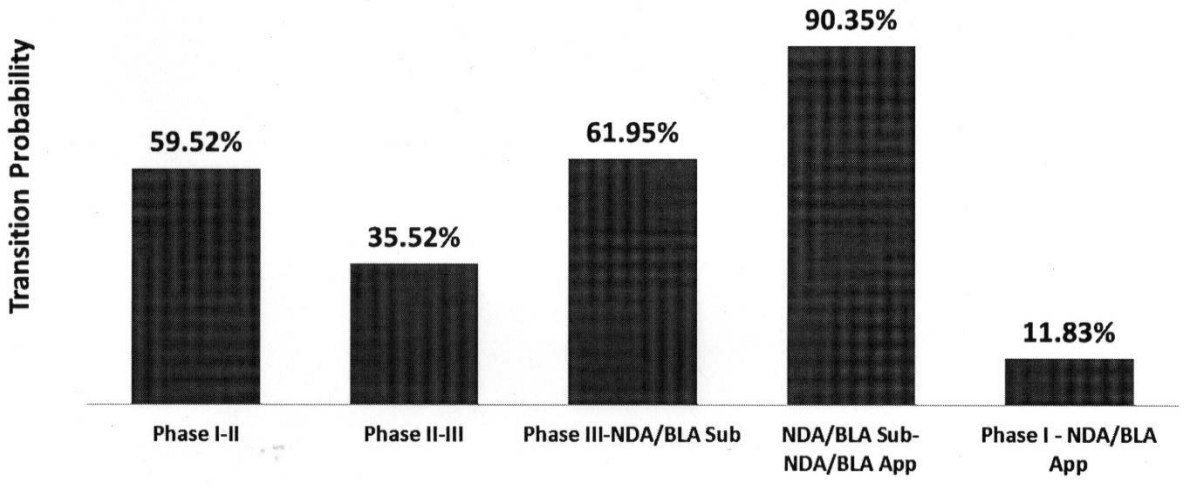
Table 1
R&D by Function, PhRMA Member Companies: 2016
(dollar figures in millions)

Function	Dollars	Share
Pre-Human/Pre-Clinical	$11,292.60	17.2%
Phase I	6,054.80	9.2
Phase II	7,426.10	11.3
Phase III	18,327.30	28.0
Approval	2,413.80	3.7
Phase IV	7,466.10	11.4
Uncategorized	12,557.60	19.2
TOTAL R&D	**$65,583.30**	**100.0%**

Notes: All figures include company-financed R&D only. Total values may be affected by rounding.

Source: Pharmaceutical Research and Manufacturers of America, PhRMA, Annual Membership Survey, 2017(B).

Figure 2
Clinical Phase Transition Probabilities and Overall Clinical Approval Success Rate*



*Therapeutic new molecular entities and new therapeutically significant biologic entities first tested in humans, 1995-2007

Source: Joseph A. DiMasi et al., "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," Journal of Health Economics, Vol. 47, 2016, pp. 20-33.

V. Regulatory Intervention

The pharmaceutical industry was restructured in 1984 by a striking exercise of industrial policy. The Hatch Waxman Act passed in that year effectively divided U.S. pharmaceutical supply into two separate and distinct industries: each with its own regulatory structure and policy objectives. The long established drug companies would comprise the branded pharmaceutical Industry, and function much as they had done before, although now faced by a strongly revised set of incentives. In addition, an entirely new industry was fashioned that was designed to compete with their branded counterparts following patent expirations. Most striking, the prospective members of the new generic industry were specifically incentivized to challenge legally the validity of existing patents held by the members of the branded industry.

Significantly, generic producers would not face the stringent FDA regulations that required extensive demonstrations of safety and efficacy. Instead, they would merely be required to demonstrate "bio-equivalence" with the original branded product. As a result, prospective entry

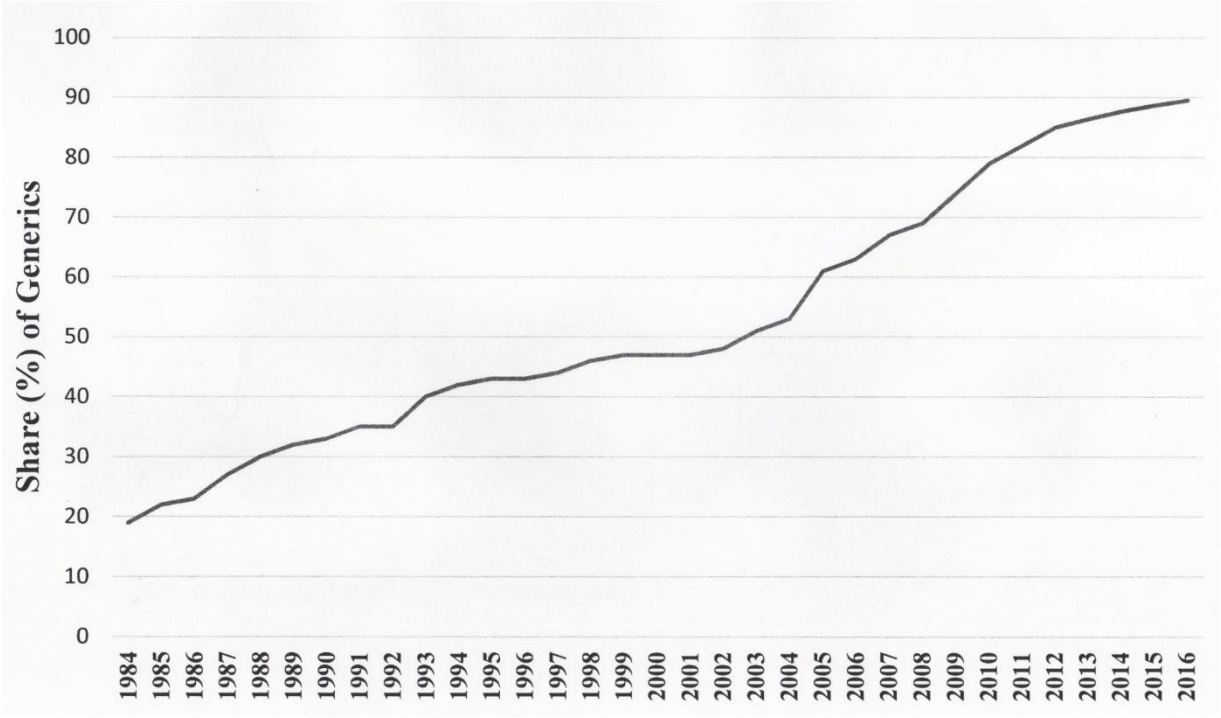
costs would decline substantially: from commonly exceeding $100 million to less than a few million dollars.[28] Generic producers would not now be required to bear the substantial costs of pharmaceutical innovation. Their mission instead would be to supply high quality products at much lower prices after the patents on branded drugs had expired.

At the time, serious questions were raised as to whether this scheme would work. Would physicians and patients trust "knock off" drugs even with FDA approval? How would established branded suppliers respond when faced by the unrestricted entry of generic producers selling their long established products? Would a policy of two distinct pharmaceutical industries, not found anywhere else, actually work? But that was 41 years ago, and now we have the answers.

See Figure 3 for data on the striking growth of the generic pharmaceutical industry. From less than 20% of retail prescriptions filled generically in 1984, this percentage has exploded to fully 90% by 2016. In a corresponding manner, the share of branded prescriptions declined to only about 10%. See Table 2 for data describing the current postures of the two industries. Despite the sharp decline in the proportion of branded pharmaceuticals prescriptions actually dispensed, the banded industry has retained fully 80% of total invoiced revenues although somewhat less when rebates and other price concessions are taken into account. The critical feature here is that average branded revenues per prescription filled in 2018 exceeded $650 while average generic revenues per prescription were less than $23. Such differences are indicative of the presence of two separate and distinct industries.

[28] Stuart O. Schweitzer & Z. John Lu, PHARMACEUTICAL ECONOMICS AND POLICY: PERSPECTIVES, PROMISES AND PROBLEMS 92 (3rd ed. 2018).

Figure 3
Percentage of Prescriptions Filled with Generic Pharmaceuticals



Source: Center for Medicare and Medicaid Services 2018, Nationl Health Expendtures by Type of Services and Source of Funds, 1960-2016.

Table 2
The Branded and Generic Pharmaceutical Industries, 2019

	Total	Branded	Generic
Dispensed Prescription (millions)	4,217.8	413.3 (9.8%)	3,804.5 (90.2%)
Total Invoice Spending ($billions)	$511.4	$409.1 (80.0%)	$102.3 (20.0%)
Total Spending after discounts, rebates and other price concessions on brands ($billions)	$356.0	$270.1	$85.9
Average Revenue per Prescription	$84.40	$653.52	$22.58

Source: IQVIA Institute for Human Data Science, *Medicine Spending and Affordability in the United States*, May 2020, pp. 6, 33.

The distinctive objectives of the two industries are also evident in international price comparisons. See the striking evidence disclosed in Table 3 that rests on price indices published by the RAND Corporation. As indicated there, U.S. branded prices are the highest among the 32 OECD countries while U.S. generic prices are among the lowest. These striking differences are the direct result of the revised regulatory environment created in 1984.

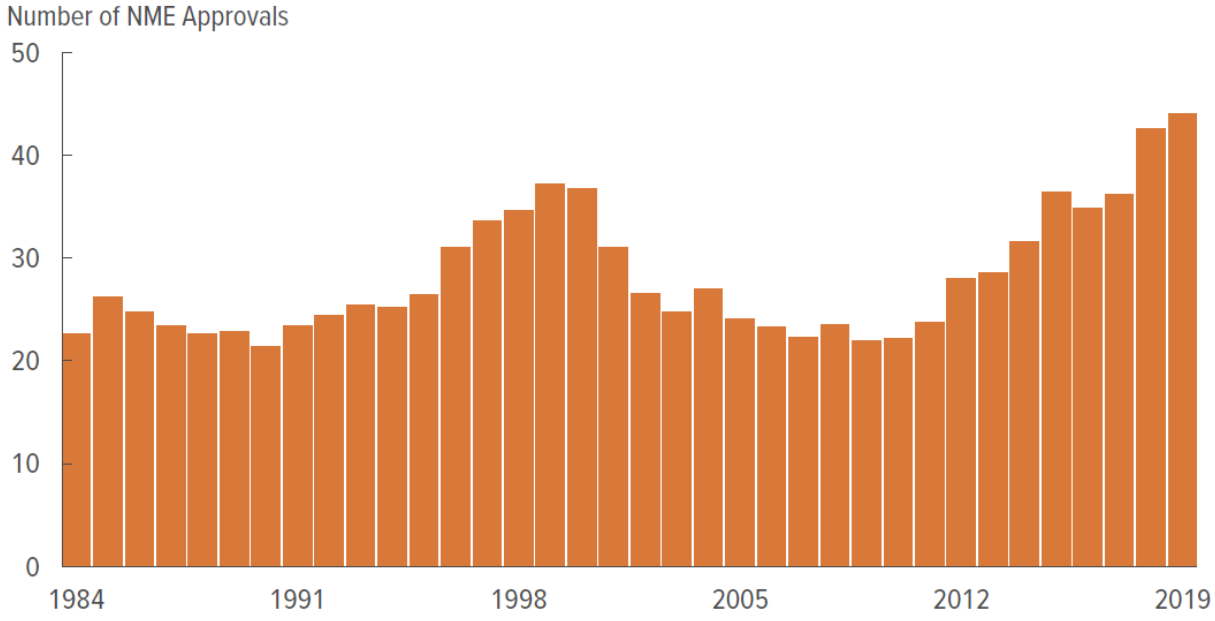
Table 3
U.S. Prices as Percentage of Other-Country Prices, RAND Sample, 2018

	Branded/Originator Drugs		
	List Prices	**Net Prices Adjustment**	**Generic Drug Prices w/o Biologics**
Canada	294%	197%	57%
France	349%	234%	58%
Germany	280%	187%	62%
Japan	307%	206%	43%
United Kingdom	349%	234%	68%

Source: A.W. Mulcahy, et al., "International Prescription Drug Price Comparisons: Current Empirical Estimates and Comparisons with Previous Studies," RAND Corporation, 2021, p. 49.

While generic prices have declined, branded prices have increased sufficiently to reward the developers of innovative pharmaceuticals. Figure 4 provides data on the recent numbers of new approved pharmaceuticals. Apparently the revised incentive structure following the Hatch-Waxman Act has not limited the search for new innovative pharmaceuticals, and may even have increased it.

Figure 4
Approvals of New Drugs
(Five-Year Moving Average)



Source: "Research and Development in the Pharmaceutical Industry," Congressional Budget Office Report, April 2021, p. 7.

An important feature of this refigured industrial structure is that R&D outlays, designed to promote pharmaceutical innovation, are entirely due to the branded industry. Strikingly, this effort is entirely supported from revenues received from only about 10% of all prescriptions filled. While the generic industry commonly sets very low prices, it engages minimally on research and development efforts designed to create new pharmaceuticals.

This unique industrial structure did not arise from industry decisions but instead was imposed by policy-makers seeking to resolve a policy conundrum. See the following passage from a legal opinion that explains the circumstances of the new law.

"The Act emerged from Congress' efforts to balance two conflicting policy objectives: to induce name-brand pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market."[29]

[29] Abbott Laboratories v. Young, 920 F.2d 984 (D.C. Cir. 1990).

As the court decision indicated, branded pharmaceutical companies were specifically tasked with promoting pharmaceutical innovation. Furthermore, the recognition of rapid generic entry following patent expiration may have reinforced the incentive of branded companies to develop new innovative pharmaceuticals. That result was particularly likely since future revenues depended fundamentally on their introducing new pharmaceuticals for which patent protection would be secured.

VI. Prices and Values of Branded Pharmaceuticals

The pharmaceutical prices considered here are those charged by drug companies, represented generally by Pharmacy Benefit Managers (PBMs), and predominantly paid by government programs and health insurance companies. Only about 5% of all prescriptions filled are entirely paid in cash by consumers.[30] In most cases, producer prices are negotiated between drug companies and insurance companies. In addition, recent government policies require substantive price negations between drug companies and Medicare on the prices to be charged for its high volume pharmaceuticals.

Not only are there differences therefore between List prices and Net prices, which are those agreed upon following negotiations, but also Insurers commonly set still lower prices to be charged to subscribers, which represents a further discount. See Table 4 for recent data on average differences among List Prices, Net Prices, and Consumer Prices for private payers. These data report median prices for a sample of 79 important branded pharmaceuticals.[31] As indicated, consumer prices on average are less than 10% of drug company list prices, but also are less than 20% of insurance company net prices. What is evident in these data is that, in large measure, high producer prices are paid collectively through insurance premiums or tax payments and not individually.

[30] IQVIA Institute for Human Data Science, *Medicine Use and Spending in the U.S.* 54 (2019).

[31] Benjamin N. Rome, MD et al., *Correlation Between Changes in Brand-Name Drug Prices and Patient Out-of-Pocket Costs*, JAMA NETW OPEN, May 4, 2021, at 5, 5.

Table 4
Branded Producer Prices and Patient Consumer Prices

	List Prices*	Net Prices*	Consumer Prices*
2015 Weighted by use	$333	$173	$29
2015 Unweighted	$691	$492	$36
2017 Weighted by use	$386	$166	$30
2017 Unweighted	$900	$489	$40

* Median prices for a 30-day supply from a sample of 79 important branded pharmaceuticals.

Source: Benjamin Rome et al., Correlation between Changes in Brand-Name Drug Prices and Patient Out-of-Pocket Costs, *JAMA Network Open*, May 4, 2021, p.5.

Still, producer prices may be high even when paid largely collectively, and there are appropriate concerns as to whether sufficient value is received. As noted earlier, a common measure of pharmaceutical value concerns individual drugs and their relation to the prices charged for them. On this point, colleagues and I explored connections between the additional QALYs gained from new pharmaceuticals and the prices charged for them.[32]

For many years, the medical literature has included a large number of cost effectiveness studies that estimated the QALYs gained from employing a new drug along with their published list prices. With considerable effort, the Tufts Center for Drug Development has constructed an extensive data set from this literature. Each data point includes both a new drug's list price and its therapeutic benefits as measured by the increased number of QALYs gained.

My research, along with colleagues, employed these data to estimate the association between List Prices and QALYs gained for a sample of 476 drug introductions between **1**994 and 2015.[33] By way of comparison, between 2014 and 2018, 219 new active substances were launched in U.S. pharmaceutical markets. We employed regression analysis to estimate the average price per QALY gained for the drugs included in our sample. Our empirical findings are reported in Table 5.

[32] H.E. Frech III et al., *Costs and Benefits of Branded Drugs: Insights from Cost-Effectiveness Research*, 13 J. BENEFIT-COST ANALYSIS 166-81 (2022).

[33] *Id.*

Table 5
Regression Models with List Prices as Dependent Variable

		Cost / QALY	Standard error	R^2
A.	All comparisons	$28,561*	($4,941)	0.20
B.	Small Molecule – No Sponsor	$13,593	($7,671)	0.25
	Small Molecule – Sponsor	$34,911*	($2,570)	
	Biological – No Sponsor	$30,182**	($9,198)	
	Biological – Sponsor	$40,370*	($10,181)	
C.	Small Molecule – Non-Cancer	$22,571*	($6,144)	0.27
	Small Molecule – Cancer	$44,367*	($4,577)	
	Biological – Non-Cancer	$42,174*	($10,769)	
	Biological – Cancer	$19,998	($11,157)	

N equals 476 Comparisons. *p<0.001; **p,0.01

Source: H.E. Frech III, Mark V. Pauly, William S. Comanor, and Joseph R. Martinez, "Costs and Benefits of Branded Drugs: Insights from Cost-Effectiveness Research," *Journal of Benefit-Cost Analysis* 13(2), 2022, pp. 166-81.

As reported there, and without any additional explanatory factors (controls), our estimated average price per QALY gained lies just under $30,000, but the equation accounts for only about one-fifth of the variation in list prices. Moreover, estimated price variations around these estimated values are also provided. The estimated coefficient's standard error is $4,941. Accordingly, by these data, 95% of alternative values are projected to lie between $18,679 and $38,443, which are plus and minus two standard errors. That range describes the broad limits within which lies the estimated average price per QALY.

When various control factors are included in the regression equations, the price estimates by themselves now explain about one-fourth of the total price variation. While the estimated average price per QALY is somewhat greater, it remains below $45,000. Of particular interest is the finding that the identification of company sponsored research is everywhere associated with higher price per QALY and not lower ones. There is no indication in these data that studies sponsored by the introducing drug company understate these estimated prices.

A frequent claim is that pharmaceutical prices are set arbitrarily and often do not reflect a drug's embodied therapeutic value.[34] To be sure, these observations do not contradict the prospect that some list prices can be quite high despite providing little commensurate therapeutic value. However, as with all averages, there must also be drugs whose prices lie below average therapeutic values per QALY.

A more fundamental question is whether prices on average that lie between $40,000 and $45,000 per QALY should be considered excessive relative to the value provided. Health analysts often use $50,000 or $100,000 per QALY as standards for determining a drug's cost effectiveness.[35] However, those figures understate available evidence on consumer preferences as revealed by their observed behavior. A comprehensive review of the associated economic literature appears in Viscusi's detailed volume [36] In addition, another valuation of statistical lives appears in a government report intended for use in regulatory decisions.[37] In both cases, the estimated values of prospective QALYs gained exceeds $200,000. In effect, therefore, both consumers and government regulators value the statistical lives gained through the introduction new pharmaceuticals at more than four times their average cost.

When branded pharmaceutical prices on average are measured relative to the medical benefits provided, their average prices are therefore not excessive. Indeed, because of the considerable variability inherent in branded drug prices, insurance policies are appropriately employed so that individual risks are spread across patients. Furthermore, the high prices charged for branded pharmaceuticals should appropriately be balanced against the low prices charged for generic pharmaceuticals, particularly when the latter account for fully 90% of all prescriptions dispensed.

VII. Financing Innovative Investments

Unlike most innovative investments, aggregate U.S. funding has long been the province of both public and private sources. In 2000, U.S. private companies accounted for 58% of the total;

[34] Rena Conti, Richard G. Frank, & Jonathan Gruber, *Addressing the Trade-Off Between Lower Drug Prices and Incentives for Pharmaceutical Innovation*, BROOKINGS INSTITUTION, (2021) at 1.

[35] Peter Neumann et al., *Updating Cost-Effectiveness: The Curious Resilience of the $50,000-per-QALY Threshold, in* 371 NEW ENGLAND JOURNAL OF MEDICINE 796-97 (2014).

[36] W. Kip Viscusi, PRICING LIVES: GUIDEPOSTS FOR A SAFER SOCIETY (2018).

[37] U.S. Dept. of Health and Human Services, GUIDELINES FOR REGULATORY IMPACT ANALYSIS (2016).

while federal and state sources add an additional 38% and Foundations and Charities another 4% of the total.[38] These amounts do not include expenditures made abroad, particularly by European companies, which also support innovative efforts. Since pharmaceutical R&D is a world-wide activity, all such expenditures support pharmaceutical innovation.

More recent data for the ten largest pharmaceutical companies are reported for 2021 in Table 6. The reported R&D budgets for these companies sum to $108 billion, which approaches 20% of aggregate revenues. Of the ten companies listed here, two are Swiss owned and two more have British origin, with the others being U.S. companies. To be sure, this number includes only ten companies and thereby understates worldwide totals. Furthermore, these numbers do not include outlays made by smaller firms, although they may include payments made directly to smaller companies who are partners of the larger firms or alliance members. Such affiliated companies have recently become common.[39]

[38] Sean Nicholson, *Financing Research and Development*, *in* THE OXFORD HANDBOOK OF THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY 47, 49 (Patricia M. Danzon & Sean Nicholson eds., 2012).

[39] William S. Comanor, *The Economics of Research and Development in the Pharmaceutical Industry, in* PHARMACEUTICAL INNOVATION: INCENTIVES, COMPETITION, AND COST-BENEFIT ANALYSIS IN INTERNATIONAL PERSPECTIVE 54, 55-66 (Frank A. Sloan & Chee-Ruey Hsieh eds., 2007).

Table 6
Largest Pharmaceutical Companies, 2021

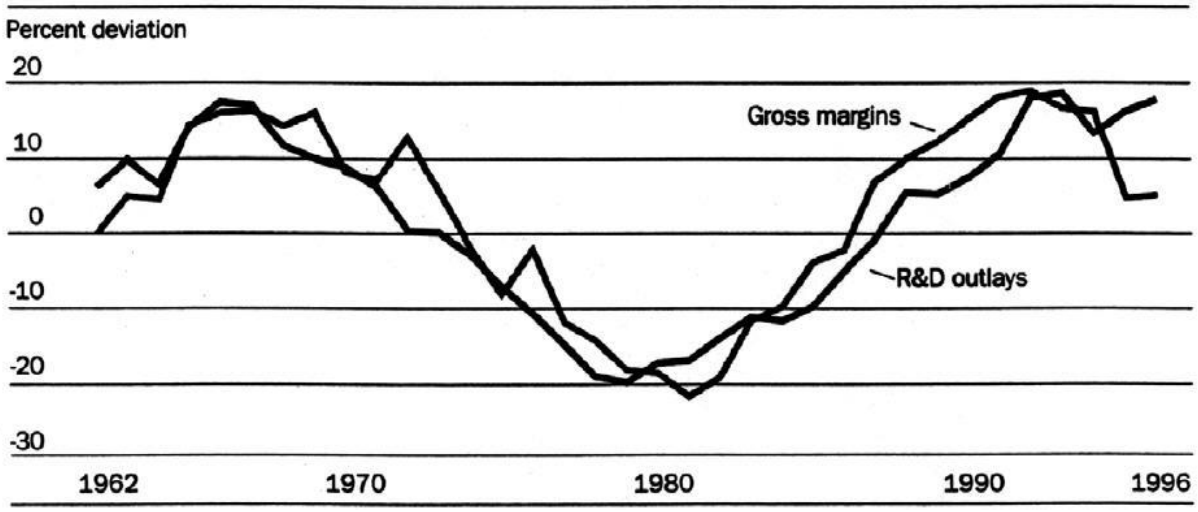
	Total 2021 revenue (Billion, 2021 USD)	R&D budget (Billion, 2021 USD)	R&D budget as percentage of revenue
Johnson & Johnson	$93.8	14.7	15.7
Pfizer	81.3	13.8	17.0
Roche (Swiss)	71.4	16.1	22.5
AbbVie	56.2	7.1	12.6
Novartis (Swiss)	51.6	9.0	17.4
Merck & Co.	48.7	12.2	25.1
Bristol-Myers Squibb	46.4	11.3	24.4
GlaxoSmithKline (UK)	46.2	7.2	15.6
AstraZeneca (UK)	37.4	9.7	25.9
Eli Lilly	28.3	7.0	24.7

Source: Security and Exchange Commission, Form 10-Ks.

For the most part, industry R&D budgets are financed from company revenues that exceed the direct costs of production and distribution. As an economic matter, these revenues are considered to be "quasi-rents" rather than monopoly profits as they are used to pay the "sunk costs" of research and development rather than representing a return on investment.

Consistent with this judgment is evidence that high drug prices and the resulting company revenues drive R&D outlays. See the data in Figure 5 which illustrates that industry gross margins and R&D outlays track each other. In effect, R&D outlays increase when margins increase, and decline when margins decline. This observation supports the judgment that company revenues exceeding direct costs are largely employed to finance their R&D along with ancillary outlays.

Figure 5
Percentage Deviations from Trend for Pharmaceutical Industry Gross Margins and Research and Development (R&D) Outlays, 1962-1996



Source: F. M. Scherer, "The Link Between Gross Profitability and Pharmaceutical R&D Spending," *Health Affairs* 20:216-220, 2001.

A frequently raised issue arises from the overlapping research efforts of drug companies and that carried out in university / government facilities, most prominently in the U.S. National Institutes of Health (NIH). In 2020, NIH funding reached $41 billion,[40] which is slightly less than half of the recent R&D expenditures reported for the ten leading pharmaceutical companies. The question here is whether research supported by tax revenues or philanthropic contributions is substitutable for that financed through the quasi-rents received by privately owned drug companies. In that case, high drug prices leading to the receipt of substantial quasi-rents might not be required for substantial pharmaceutical innovation. However, that perspective requires that government / philanthropic R&D efforts be sufficiently similar in purpose and effect to the R&D financed by private companies such that they be highly substitutable. .

Such comparisons can be misleading because they do not account for acknowledged differences between the distinctive purposes of industry and university/government research efforts. Recall that pre-human/pre-clinical outlays represent only about 17% of total industry R&D. In contrast, the largest share of industry efforts is directed towards the support of specific

[40] U.S. Congressional Budget Office, RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 18 (2021).

prospective pharmaceuticals. To be sure, research can yield both scientific knowledge and support a new technology.[41] For this reason, there may not be a sharp line between the two realms of scientific effort. However, what can be distinguished are the different objectives that underlie the two areas of research.

A recent study compared research productivities as between drug company R&D outlays and NIH (government) funding.[42] Although many pharmaceutical innovations may rely on scientific discoveries made at the NIH or universities; that connection does not mean that NIH funding is a sufficient factor leading to pharmaceutical innovation. Indeed, these authors found that company efforts are the costlier segment of innovative drug development. Their study concluded: "one NME (new medical entity) worth of additional private R&D investments ($270 million) is equivalent to about $1 billion in NIH funding."[43] The implication is that once basic discoveries are made, more focused R&D efforts are commonly required before a new pharmaceutical can be developed, tested and submitted for approval to the Food and Drug Administration

The connection between public and private R&D was also explored in a study by Toole.[44] He reported that for every public dollar allocated to basic biopharmaceutical research, an additional $8.38 is spent on industry R&D.[45] On a similar point, a report by the National Academy of Sciences (NAS) observed that "Researchers involved in basic research are often poorly positioned to develop their findings into a commercially viable product."[46]

On these issues, a recent Congressional Budget Office Report concluded that "the complementary relationship between public and private R&D spending arises mainly because NIH funding focuses on basic research … whereas private spending focuses on applications of such research."[47] As is appropriate, the two types of activities are funded differently: university/

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[41] Fiona Murray & Scott Stern, *When Ideas Are Not Free: The Impact of Patents on Scientific Research, in* INNOVATION POLICY AND THE ECONOMY, VOLUME 7 33-69, 62 (Adam B. Jaffe et al. eds. 2007).

[42] Kyle Myers & Mark Pauly, *Endogenous Productivity of Demand-Induced R&D: Evidence from Pharmaceuticals, in* 50 THE RAND JOURNAL OF ECONOMICS (Fall 2019) 591-614.

[43] *Id.* at 605.

[44] Andrew A. Toole, Does Public Scientific Research Complement Private Investment in Research and Development in the Pharmaceutical Industry?, 50 J. OF LAW & ECON. 81-104 (2007).

[45] *Id.*

[46] NATIONAL ACADEMY OF SCIENCES, MAKING MEDICINES AFFORDABLE: A NATIONAL IMPERATIVE 32 (2018).

[47] U.S. Congressional Budget Office, *supra* at 19, 39-40.

government efforts that are directed at more scientific issues is largely funded through tax revenues, while industry efforts that are directed towards developing new pharmaceuticals are financed by private revenues that exceed direct costs.

VIII. The Normative Theory of Pharmaceutical Innovation

This theory was laid out succinctly in a chapter by Lakdawalla and Sood[48] so this discussion follows their account. An investment in innovation such as that made by branded pharmaceutical companies turns on the expected financial gains resulting from successful innovation. Economic efficiency requires that an innovator bear the full cost of the innovation but can also fully appropriate its benefits as represented by the incremental consumer surplus gained.[49]

In the presence of heterogeneous consumers (patients), an innovator would find it difficult to extract the full measure of this surplus when the same prices are charged to everyone. In that case, considerable consumer surplus would remain that is available to consumers but not to the innovator. As a result, the perspective rewards from an innovative pharmaceutical would lie below its full value so that insufficient resources would be directed towards innovative efforts. As these authors emphasize, "the under-provision of innovation relies on the inability of the innovator to capture the full value of social surplus."[50]

Another relevant concern affecting innovative incentives is that the ultimate beneficiaries of pharmaceutical innovations do not fully determine the "willingness to pay" amounts for the innovative outcome. Instead, public and/or private payers play that role in their negotiations over the prices to be paid to innovative suppliers. While it can be argued that well-functioning insurance markets will set premiums that reflect consumers' willingness to pay amounts, that supposition may be misleading. Not only are pharmaceuticals commonly a minor component of most health insurance premiums but also payers' prospective revenues may take priority in their price negotiations with drug companies. Although consumer preferences may affect the agreed upon prices, they are not likely to be determinative.

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[48] Darius Lakdawalla & Neeraj Sood, *Incentives to Innovate*, THE OXFORD HANDBOOK OF THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY 143-66 (Patricia M. Danzon & Sean Nicholson eds., 2012).

[49] *Id.* at 156.

[50] *Id.* at 157.

Even when the social value of an innovation exceeds its corresponding private benefits, there still remain incentives for innovation. As Scherer pointed out, private sector investments are driven by demand conditions but also by the fecundity of the science base.[51] Both factors can impede or promote innovative efforts even when they fall short of reaching the social optimum. While innovative efforts continue, various factors intrude to suggest they provide less than socially optimal outcomes.

IX. Global R&D Costs and Benefits

The information generated by pharmaceutical R&D, whether publicly or privately financed, represents a classic example of a Public Good. Its use by one party in the absence of patent protection does not limit its value to others. To be sure, specific information created by individuals or firms is sometimes hidden from public view, but any effort in that direction runs counter to the incentive structure created by the current patent system. In return for full disclosure of the prospective applications of the information created, its creator is granted full legal right to all applications of the information created along with the right to acquire its maximum value.

To be sure, patent rights expire twenty years after discovery, subject to potential additional time under current legislation. After that time has elapsed, whatever information has been generated through the R&D process becomes available for use by all, including those who contributed nothing to its creation. This feature of the patent system provides a necessary condition for the generic pharmaceutical industry. Upon patent expiration, the information generated by branded firms becomes available for use in the generic industry.

Another feature of pharmaceutical innovation process is that the returns to innovation can vary substantially across countries despite being founded on the same technical information. When the prices charged for patented pharmaceuticals differ, so do the aggregate returns from innovation. Indeed, where prices are relatively high, so are the returns from innovation, while these returns are much lower where prices minimally exceed direct costs.

Most significant is the recognition that full returns from innovation rest on aggregate net revenues from all counties where pharmaceuticals are sold. As a result, total discovery costs of

[51] F.M. Scherer, *Pharmaceutical Innovation*, *in* 1 HANDBOOK OF THE ECONOMICS OF INNOVATION 539-74, 566 (Bronwyn H. Hall & Nathan Rosenberg eds., 2010).

creating innovative pharmaceuticals are financed by global quasi-rents that rest on the international distribution of prices. Where prices are low but still cover country-specific production and distribution costs, there are then lower returns from innovation. In contrast, relatively high prices in relation to country-specific costs cover the predominant share of the aggregate cost of innovation. Countries with the highest prices provide the primary incentive to develop innovative pharmaceuticals.

In recent research, colleagues and I estimated the pharmaceutical quasi-rents received in the 32 OECD countries.[52] These estimates rest on a recent RAND Report[53] that calculates price indices for branded pharmaceuticals after correcting for rebates and discounts. We then linked these price indices with available data on national sales, and also estimated marginal costs assumed to be the same for all OECD countries. From these data, we computed national contributions in 2018 to the global public good of scientific information leading to innovative pharmaceuticals. See Table 7 for the computed estimates.

[52] H. E. Frech, III et al., *Pharmaceutical Pricing and R&D as a Global Public Good* (Nat'l Bureau of Econ. Rsch., Working Paper No. 31272, 2023).

[53] Andrew W. Mulcahy et al., INTERNATIONAL PRESCRIPTION DRUG PRICE COMPARISONS, RAND Research Report (2021).

Table 7
International Support for
Pharmaceutical R&D: 2018

Support levels derived from data on international prices available in the RAND Report that exceed estimated direct costs of production and distribution.

All OECD Countries	$400 billion	---
United States	$280 billion	$884 per capita
Japan	$29 billion	$227 per capita
Germany	$16 billion	$198 per capita
France	$10 billion	$143 per capita
UK	$7 billion	$110 per capita
Switzerland	$2 billion	$263 per capita

Source: H.E. Frech, M.V. Pauly, W.S. Comanor, J.R. Martinez, "Pharmaceutical Pricing, and R&D as a Global Public Good," NBER Working Paper 31272, May 2023.

As reported there, U.S. contributions are far greater than all other OECD countries due both to its much higher prices and larger population. However, the contributions of other large counties are not inconsequential. The U.S. estimated contribution represents 72% of the total support for developing innovative pharmaceuticals. That estimate still leaves over one fourth of the R&D burden to others. The next largest contributors are Japan that accounts for 7% and Germany that accounts for 4%.

On a per-capita basis, the US contribution of $884 per capita is much greater than elsewhere. Its average contribution to innovative pharmaceuticals is over three times the next largest contributor, which is Switzerland at $263 per capita. In effect, the United States largely but not entirely provides the support and incentive for pharmaceutical innovation.

X Economic Conclusions

In the absence of a dominant overall authority, public goods are widely acknowledged as undersupplied, indicating their availability falls below the social optimum. Because the therapeutic information leading to pharmaceutical innovation is a global public good, it follows that insufficient resources are devoted internationally towards discovering the next generation of new and improved pharmaceuticals.

That conclusion is not a recent one. Indeed, its theoretical foundation was developed in Olson's classic treatise that was published more than 50 years ago. His work emphasized that economic forces lead "small groups towards a sub-optimal provision of collective goods." And also that "the larger the number in the group, …the more serious the sub-optimality will be."[54] Because such goods are available to all users, many are incentivized to "free ride" on the efforts of others. As applied to the R&D efforts supporting pharmaceutical innovation, this effect is clearly demonstrated in Table 7.

The undersupply of public goods results from the economic incentives that are invariably present. When someone else is carrying much of the load, that factor impacts one's own decision making. While such actions go by the pejorative term of "free riding," it simply represents rational decision-making in the presence of the anticipated actions of others.

Olson also recognized a second attribute of public goods that is also relevant here. As he emphasized, and is now widely recognized, the user with the greatest prospective benefit derived from the public good "will bear a disproportionate share of the burden." That acknowledged feature of public goods is commonly referred to as the "exploitation of the great by the small."[55] Since support for providing this public good is determined largely by the quasi-rents received from national sales of branded pharmaceuticals, the higher prices and quantities found in the United States are entirely consistent with Olson's Exploitation hypothesis.

[54] Mancur Olson, THE LOGIC OF COLLECTIVE ACTION: PUBLIC GOODS AND THE THEORY OF GROUPS 28 (1965 & 1971).

[55] *Id.* at 29.

Stiglitz's early paper on global public goods[56] is also insightful. He acknowledges that knowledge / information is a public good in that its use by one user does not impede its use by others. In these circumstances, "attempts to appropriate its returns may significantly slow the overall pace of innovation."[57] In seeking to maximize national well-being, he recognized that "some countries may try to free-ride on others, …[and] "may see their self-interest enhanced more by taking out of the global knowledge commons than contributing to it."[58] As a result, aggregate support for pharmaceutical R&D is diminished, and so also is the pace of health-promoting innovation.

XI Policy Conclusions

Because global public goods, supported nationally, are invariably undersupplied, policy makers should explore the probable gains from international cooperation. As others have concluded, efforts should be made to lead other wealthy countries to shoulder more of the burden in support of medical / pharmaceutical innovation.[59] Current outcomes could be improved through international agreements. Increased international efforts in this realm would promote enhanced global public health.

[56] Joseph E.Stiglitz, *Knowledge as a Global Public Good*, *in* GLOBAL PUBLIC GOODS: INTERNATIONAL COOPERATION IN THE 21ST CENTURY (Inge Kaul et al. eds.,1999), http://pinguet.free.fr/stiglitz1999.pdf

[57] *Id.* at 5.

[58] *Id.* at 11.

[59] Dana Goldman & Darius Lakdawalla, *The Global Burden of Medical Innovation*, Brookings Institution (2018).

REFERENCES

Abbott Laboratories v Young, 920 F.2d 984; (1990)

Agrawal,Virat, Neeraj Sood, Christopher M. Whaley, *The Impact of the Global COVID-19 Vaccination Campaign on All-Cause Mortality,* USC Price School of Public Policy, 2024.

Buxbaum, Jason D., Michael E. Chernew, A. Mark Fendrick, and David M. Cutler, "Contributions of Public Health, Pharmaceuticals, and other Medical Care to US Life Expectancy Changes 1990-2015," *Health Affairs*, 39(9) (2020): 1546–1556.

Comanor, William S., Research and Technical Change in the Pharmaceutical Industry, *Review of Economics and Statistics*, XLVII, May 1965, pp. 182-190.

Comanor, William S., The Economics of Research and Development in the Pharmaceutical Industry, Ch. 3, *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective,* edited by F.A. Sloan and CR Hsieh, Cambridge University Press, 2007.

Comanor, William S., Stuart O. Schweitzer, Jon Riddle, Frederic Schoenberg, "Value Based Pricing of Pharmaceuticals in the US and UK: Does Centralized Cost Effectiveness Analysis Matter?," *Review of Industrial Organization*, February 2018, Vol. 52, p. 502.

Conti, Rena, Richard G. Frank, and Jonathan Gruber, "Addressing the Trade-off between lower drug prices and incentives for pharmaceutical innovation," Brookings Institution, November 15, 2021, p.1.

Covid Mortality Collaborators, "Estimating excess mortality due to the Covid-19 Pandemic: a systematic analysis of Covid-19-related mortality," The Lancet, Vol. 399, 2022, pp. 1513-1536.

DiMasi, Joseph A., Henry G. Grabowski, and Ronald W. Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," *Journal of Health Economics*, Vo. 47, May 2016, pp. 20-33.

Frech, H.E., Richard Miller, *The Productivity of Health Care and Pharmaceuticals: An International Comparison*, AEI Press, 1999.

Frech, H.E, Mark V. Pauly, William S. Comanor and Joseph R. Martinez Costs and Benefits of Branded Drugs: Insights from Cost-Effectiveness Research," *Journal of Benefit-Cost Analysis* 13(2), 2022, pp. 166–181.

Frech, H. E., Mark V. Pauly, William S. Comanor and Joseph R. Martinez, "Pharmaceutical Pricing, and R&D as a Global Public Good," 2023, NBER Working Paper 31272.

Goldman, Dana and Darius Lakdawella, "The Global Burden of Medical Innovation," Brookings Institution, January 2018.

IQVIA Institute for Human Data Science, "Medicine Use and Spending in the U.S.," May 2019, p.54.

Kaestner, R., M. Darden, D. Lakdawalla, "Are Investments in Disease Prevention Complements? the Case of Statins and Health Behavior," *Journal of Health Economics*, Vol.36, 2014, pp. 151-163

Lakdawalla, Darius, Neeraj Sood, Incentives to Innovate, *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, 2012, Ch.6, pp. 143-166.

Lichtenberg, Frank R., "Pharmaceutical Knowledge-Capital Accumulation and Longevity," *Measuring Capital in the New Economy*, University of Chicago Press, 2005, 237-274.

Miller, Richard D, H.E. Frech III, *Health Care Matters: Pharmaceuticals, Obesity, and the Quality of Life*, AEI Press, 2004.

Mulcahy, Andrew W., Christopher M. Whaley, Mahlet Gizaw, Daniel Schwam, Nathaniel Edenfield, and Alejandro Uriel Becerra-Ornelas, "International Prescription Drug Price Comparisons," RAND Research Report, 2021.

Murray, Fiona, Scott Stern, "When Ideas Are Not Free: The Impact of Patents on Scientific Research," *Innovation Policy and the Economy*, *Volume 7*, NBER, 2006, pp. 33-69.

Myers, Kyle and Mark Pauly, "Endogenous Productivity of Demand-Induced R&D: Evidence from Pharmaceuticals," *The RAND Journal of Economics*, Vol. 50, No. 3, Fall 2019, pp. 591-614.

National Academy of Sciences, *Making Medicines Affordable: A National Imperative*, National Academies Press, 2017.

Neumann, Peter, Joshua T. Cohen, and Milton C. Weinstein, "Updating Cost-Effectiveness: The Curious Resilience of the $50,000-per-QALY Threshold," *New England Journal of Medicine*, Vol. 371 No. 9, August 28, 2014, pp. 796-797.

Neumann, Peter, Joshua T. Cohen, Daniel A. Ollendorf, *The Right Price: A Value-Based Prescription for Drug Costs*, Oxford University Press, 2021.

Nicholson, Sean, Financing Research and Development, *The Oxford Handbook of The Economics of the Biopharmaceutical Industry*, 2012, Ch.3, p.47.

Nicholson, Walter, Christopher Snyder, *Microeconomic Theory: Basic Principles and Extensions*, 12th ed., 2016, p. 696.

Nordhaus, William D., 2004, Schumpeterian Profits in the American Economy, NBER Working Paper 10433.

Olson, Mancur, *The Logic of Collective Action: Public Goods and the Theory of Groups*, Harvard University Press, 1965, 1971

Philipson, Tomas and Anaupam B. Jena, "Who Benefits from New Medical Technologies? Estimates of Consumer and Producer Surpluses for HIV/AIDS Drugs," *Forum for Health Economics & Policy*, 9(3) (2006): 1-33.

Rome, Benjamin N., William B. Feldman, Rishi J. Desai, Aaron S. Kesselheim, "Correlation Between Changes in Brand-Name Drug Prices and Patient Out-of-Pocket Costs," *JAMA Network Open*, Vol. 4, No. 5, May 4, 2021.

Scherer, F.M., The Link between Gross Profitability and Pharmaceutical R&D Spending, *Health Affairs*, 2001, 20:216-220.

Scherer, F.M., Pharmaceutical Innovation, *Handbook of the Economics of Innovation*, Vol. 01, 2010, pp. 539-574.

Schlander, Michael, Karla Hernandez-Villafuerte, Chih-Yuan Cheng, Jorge Mestre-Ferrandiz, and Michael Baumann, "How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment," *PharmacoEconomics*, 2021, 39:1243-1269.

Schweitzer Stuart O., Z. John Lu, *Pharmaceutical Economics and Policy: Perspectives, Promises and Problems*, 3rd ed., 92, 2018.

Stiglitz, Joseph, "Knowledge as a Global Public Good," in Inge Kaul et al., *Global Public Goods: International Cooperation in the 21st Century*, 1999, http://pinguet.free.fr/stiglitz1999.pdf

Toole, Andrew A., "Does Public Scientific Research Complement Private Investment in Research and Development in the Pharmaceutical Industry?" *Journal of Law and Economics*, 2007, 50: 81-104.

U.S. Congressional Budget Office, Research and Development in the Pharmaceutical Industry, April 2021.

U.S. Constitution, Article 1, §8.

U.S. Council of Economic Advisors, Reforming Biopharmaceutical Pricing at Home and Abroad, Feb. 2018.

U.S. Department of Health and Human Services, Guidelines for Regulatory Impact Analysis, 2016.

Viscusi, W. Kip, *Pricing Lives: Guideposts for a Safer Society*, Princeton University Press, 2018.

Wouters, Olivier J., Martin McKee, and Jeroen Luyten, "Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018," *JAMA*, March 3, 2020, 323:9, pp. 844-853.