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# Striking a balance

Drug prices, profits and incentives for innovation

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This is a summary of a conference convened by the [Hutchins Center on Fiscal & Monetary Policy](#) at the Brookings Institution on March 15, 2019, with support from [Arnold Ventures](#) (formerly the Laura and John Arnold Foundation). This conference was held under Chatham House rules, but the presenters agreed to be identified.

This report is available online at: <https://www.brookings.edu/research/striking-a-balance-drug-prices-profits-and-incentives-for-innovation/>



Hutchins Center  
on Fiscal & Monetary Policy  
at BROOKINGS

# Opening Remarks: [Louise Sheiner](#)

## [Louise Sheiner's slides](#)

Louise Sheiner of the Brookings Institution's Hutchins Center on Fiscal and Monetary Policy stated that the goal of the conference was to have a wide-ranging discussion among the various stakeholders in attendance of policies to lower prescription drug prices without unduly harming innovation. She thanked the Arnold Foundation (at the time; now Arnold Ventures) for the idea to hold the conference and the funding to support it. She then provided an overview of the issues to be discussed in each of the three sessions.

## Overview of Session 1: Discussion of the social value of new drugs being developed

Sheiner noted that economists don't really know whether drug prices are too high, making policies aimed at lowering them hard to evaluate from a social welfare perspective. Higher prices increase the incentive for investment in new drug development, but also create affordability problems, resulting in less access to drugs or to health insurance more broadly (if high drug prices raise insurance premiums). One question, then, is whether the drugs that are developed on the margin are worth their cost. If consumers' willingness to pay for drugs exceeds the marginal value they get from them (perhaps because of insurance coverage, mandated drug coverage, or physician preferences), then lowering drug prices and lowering innovation at the margin could improve overall welfare.

Another key question in thinking about whether drug prices are too high is the extent to which innovation would respond to changes in prices. If innovation is limited by the number of scientists or by NIH funding, or if it is motivated by non-pecuniary rewards, then lowering drug prices wouldn't lead to fewer discoveries; it would simply lower profits in the pharmaceutical industry. On the other hand, there are reasons to believe that drug prices aren't high enough. The monopoly provided to pharmaceutical companies, through patents and exclusive marketing rights, is time-limited, meaning that some types of investments that might produce drugs whose value exceed their cost of development might not be pursued. Raising the return to these types of investment could improve social welfare.

## Overview of Session 2: Discussion of Louisiana's innovative Hepatitis C model

While these prices create profits that enable pharmaceutical companies to recoup their investments, the high prices put the drugs out of reach for many patients. Although developing new drugs entails large fixed costs, producing more of them is generally relatively cheap. Thus, some kind of two-part pricing scheme, whereby the firm charges the monopoly price on the monopoly quantity of drugs, and then a lower price on any additional quantity of drugs sold, can benefit both the drug provider and the consumer. There are many variants on this two-part pricing scheme, all of which involve negotiation over both prices and quantities. One prominent example is the innovative model developed by the state of Louisiana to

deal with the development of drugs like Sovaldi and Harvoni to cure Hepatitis C. Sheiner noted that, although at current market prices these cures are believed to save money over the long run, poor states like Louisiana that have to balance their budgets annually are unable to afford treatment for most of the Hepatitis C patients in their care (Medicaid beneficiaries and state prisoners, for example). Thus, there is the potential for negotiations between the drug manufacturers and the state to benefit both parties, with the drug manufacturers selling more drugs than they otherwise would, and Louisiana able to treat more patients.

## Overview of Session 3: Discussion of incentive distortions arising from the current patent and market exclusivity system for new drugs

Sheiner noted that the question of whether drug prices are too high is probably too broad to be answered with a simple yes or no. Drug prices in some areas may be too high, because the kinds of innovation being developed are not worth their cost, but too low in others. In particular, the paper by Heidi Williams of MIT discusses why there might be too little R&D devoted to treating diseases with long survival times. Because the FDA generally requires clinical trials proving a drug's effectiveness be completed before a drug is approved, drugs for which clinical trials are long are more costly and effectively shorten the exclusivity period for innovating firms. This is particularly a problem for drugs aimed at treating diseases with long survival times, as it takes many years to know whether these drugs are effective. The de facto requirement that diseases with longer survival time have longer clinical trials means that drug companies have much greater incentives to invest in treating diseases with short survival times, leaving some diseases under-researched relative to the social optimum. Because of this, Williams did not advocate lengthening exclusivity periods (which would increase R&D incentives for all drugs) but rather for ways to shorten clinical trials. One such option is by finding ways to increase the use of surrogate endpoints, biological markers that show a drug is working and that can proxy for the ultimate clinical endpoint (remission from cancer or death, for example). In addition, Williams thought that tax credits for research in diseases with long survival times might be useful.

## Session 1

Presentations from [David Cutler](#) and [Gerard Anderson](#)

[David Cutler's slides](#)

[Gerard Anderson's slides](#)

David Cutler of Harvard University sought to answer whether there is currently too little or too much innovation in the pharmaceutical arena. He split drugs into three categories: those that are actively helpful and provide a consumer surplus (i.e. the benefits are worth the costs), those whose price equates, more or less, to their total benefit, and those that actively do harm. In the first category, Cutler put Hepatitis C drugs and drugs used to treat cardiovascular disease. He noted that the elderly, who often suffer from cardiovascular disease, have seen a slower rate of growth of real per capita health spending than had been projected in the late 1990s and early 2000s. At the same time, hospitalization rates for

patients with cardiovascular diseases, both with and without a prior history, had fallen since the later 1990s. Cutler's [research](#) shows that these drugs had improved health outcomes for the elderly population without significantly increasing costs. For the second and third categories, Cutler used a tool from the Sloan Kettering Drug Pricing Lab, a [drug price abacus](#), where one can evaluate the price of a drug relative to its social benefit. According to those statistics, there are numerous drugs whose marginal value are at or below their marginal cost. Cutler cited opioids as a prime example of the type of drug that is actively harmful and not worth the cost.

Cutler also spoke about 'Me-Too' drugs, new drugs that are chemically or structurally similar to existing drugs. In general, the benefit of these drugs is the competition they bring to the market, rather than an improvement in treatment technology. Greater competition initially transfers rents from pharmaceutical companies to consumers. While there can be distributional consequences of this transfer, there is no welfare gain if there is no change in access or affordability. However, the greater access to drugs that should come from sufficiently lower prices spurred by competition should lead to an overall gain in welfare. This is an important distinction. Most of the increases in net social welfare come from increased access rather than lower costs. The costs of this welfare gain stem mostly from the cost of R&D necessary to create the new drugs, but the size of the tradeoff is unclear and often poorly measured. Cutler's [research](#) shows that between 2008 and 2016, much of the increase in costs for brand name drugs was due to higher prices, while increases in the costs of generics and specialty drugs was due to the introduction of new drugs.

Gerard Anderson of the John Hopkins Bloomberg School of Public Health focused on financing R&D and innovation in pharmaceuticals. In particular, he noted that the sunk costs of R&D should not be treated as a justification for price increases on the margin, since the costs already have been incurred by companies. This is, however, the reason often used in political conversations, particularly by pharmaceutical lobbyists. Citing statistics from the [Tufts Center for Drug Development](#), Anderson noted that real R&D costs have increased by 7.9% per year since the 1990s, to \$2.6 billion in 2014. According to the study, about 40% of this is the cost of capital, which is priced at about 10.5%. The direct cost of developing a drug is therefore closer to \$1.3 to \$1.6 billion, including the cost of failed drug trials. Anderson expressed concern that this money may not be spent directly on R&D, i.e. on more scientists and equipment. Anderson has [asked the House Oversight Committee](#) to review drug companies' proprietary information on how R&D money is actually spent. His [previous research](#) had found that the U.S. spends more on pharmaceuticals per capita than other OECD countries related to reasons other than actual drug innovation.

Anderson noted that R&D isn't done in-house at large pharmaceutical companies, but is done by others and purchased later. A lot of early-stage drug research is done at academic medical centers financed by government grants. Smaller venture-backed biotech firms carry out phase 1 and phase 2 drug trials. Large drug companies later purchase the drug, carry out or finish phase 3 trials, and market and sell the drug. Anderson cited Gilead and its Hepatitis C drug, Sovaldi. In the case of Sovaldi, researchers at Emory University carried out the basic research, which was funded by NIH. Venture capital firms financed the next round of research and drug trials under a spin-off known as Pharmasset. NIH and venture capital funds invested about \$200 million each in the company. Gilead purchased Pharmasset in 2012 for about \$10 billion. Anderson questioned whether this form of financing was optimal, whether it sways researchers to pursue one type of drug or form of research over another, and whether this structure has essentially led to a bidding war for promising drugs. In particular, while some premium on the drug is

needed to cover the larger fixed costs of financing R&D and failed drug trials, the large profit margin in the case of Sovaldi implies that substantial rents are being extracted.

Anderson offered several possible policy responses. One option would be limits on the portion of a drug's purchase price that is tax-deductible. Another would be for the government to seek a price reduction on a final drug if the government had a role in financing early stages of research. [The Bayh-Dole Act](#) provides a way for the government to receive a price reduction, but all five requests made to NIH on these grounds have been rejected. Changes to such a policy should consider whether the policy would affect the choice of research for NIH-funded grants, as well as what the appropriate return on investment should be for NIH-funded research.

Anderson cited drugs for rare diseases, sometimes referred to as orphan drugs, as an example of a policy success, at least in part. Drugs are available to treat only about 5% of the roughly 5,000 rare diseases – defined by the government as affecting fewer than 200,000 people in the U.S. To incentivize research, the Hatch-Waxman Act offers a 25% tax credit on R&D ([cut](#) from 50%, as part of the Tax Cuts and Jobs Act) and longer market exclusivity for orphan drugs. Orphan drug approvals have tripled since 1980.

Nevertheless, there are still many diseases without drugs, and many of the orphan drugs that do make it to market turn out to be blockbusters. Six of the top ten selling drugs in Medicare have orphan designations. The [average cost](#) of developing an orphan drug is about \$19 million, with wide variation. Costs are significantly lower for more successful drugs since they have shorter trials and have the potential for about \$2 billion in revenue. Orphan drugs can be especially profitable since pharmacy benefit managers (PBMs) usually put only one drug on their formulary, and doctors may hesitate in prescribing generics for orphan drugs due to fear of malpractice. Therefore, there seems to be a bias towards large blockbuster drugs with huge profit margins with orphan status—potentially not the best way to encourage broad innovation.

## General Discussion

While Me-Too drugs can drive up prices without providing as much value add, several participants noted that Me-Too drugs sometimes provide [additional benefits](#) outside of the existing drugs, particularly if they cater to a broader range of patients. For example, some Me-Too antidepressants are more like new drugs, since they may work for a subset of patients where the existing drug does not; for these type of Me-Too drug trials, biomarkers help predict how different patients will react. Some argued that many drugs are mislabeled as Me-Too drugs when these new drugs in fact have different characteristics and receptors. There are benefits to having multiple options to treat the same disease, since this may allow for treatment of a heterogenous patient population. Indeed, many drugs in production that end up as Me-Too drugs may not have been intended to be such. Similarly, some Me-Too drugs are improvements over existing drugs (more like 'Me-Betters') based on other metrics. They may, for instance, be taken fewer times a day and thus patient adherence may be better, a quality increase that could go unmeasured.

In discussing tradeoffs between regulation and future innovation, some participants noted that certain policies may meaningfully reduce innovation and investment in new drugs by reducing the marginal incentive to invest in R&D. Such policies might include shorter patent life, taxes on drug profits, and mandated payments to NIH for funding initial research. A second type of regulation, though, may affect the profits of pharmaceutical companies without harming the marginal return to innovation—for example, getting rid of tax write-offs for research into new drugs or increasing the corporate tax rate. In

other words, it's possible to tax rents, reduce deadweight loss, and increase access without affecting the quantity of useful drugs being produced on the margin. In many cases, firms do not appear to be meaningfully cash constrained, so if policymakers avoid affecting the return on investment on the margin, they can still regulate prices without decreasing innovation.

On innovation, some participants pointed to flaws in the FDA's [benefit and risk framework](#) for drug approval, noting that the focus is on the 'indicated patient' for a certain drug rather than on the entire population with a given disease. For example, a drug that decreases the probability of a heart attack on the margin and therefore saves thousands of lives each year might get less attention from the FDA than a drug that definitively saves a few lives by curing a particular disease. This creates distortions in the incentive for regulation. In addition, the regulatory framework does not focus on the negative externalities of drug approvals, with opioids being the most obvious example.

One open question: If a change in regulation led to less R&D, would that lead to less overall innovation? In other words, are firms at the flat end of the R&D supply curve, where small changes in investment have little effect? There were also questions about the amount of rent being extracted by large pharmaceutical companies. Several participants noted that R&D costs (equipment, scientists, etc.) are relatively low, but real R&D spending has increased on net over the past few decades. This begs the question as to where the money is being spent—for example, on [protecting intellectual property](#) rather than on innovation that acts to extract monopoly rents.

Despite the potential for large rents, participants noted that other firms participating in the R&D process, particularly small venture capital-funded biotech firms, require a higher return due to the considerable amount of risk involved at early stages of R&D. Many of these firms aren't extracting rents and may be run by former scientists who need financial incentives to provide proof of concept for certain drugs. Changes in the marginal return of R&D therefore could meaningfully shift investment flows into these small firms. Due to the lack of data on R&D costs, it was noted that it is difficult to assess what return on investment would be reasonable for the R&D process for different firms, particularly to cover the cost of failed drug trials.

More generally, there was broad agreement on the lack of available data or standards for measurement in health overall. On the demand side, quality adjustments and value of life calculations are not standardized, but can dramatically influence the price of a drug, particularly in insurers' negotiations over prices with drug manufacturers. Existing measures of quality, for example, may be too generalized: the value of one more year of additional life for a terminally ill patient may be lower than reducing the probability of a cardiac event for a prime age person who can return to work. The [SEER](#) database was mentioned as a good source of drug data. It suggests that the median drug is providing a relatively high value on a quality-adjusted cost basis.

Beyond the costs and incentives for future R&D, there was also discussion of consumer price elasticity, and how much price changes would affect access. It was noted that, given how low utilization is of clearly beneficial drugs, any policies that could increase underused drug use would provide huge value, particularly since they could allow producers to lower prices by increasing volume (a foreshadowing of the [Hepatitis C program](#) in Louisiana in the second session). It was suggested that currently, many consumers are price insensitive, since pharmaceutical companies provide coupons and patient assistance programs so that patients don't directly bear the cost of drugs. However, some old data suggests that increasing the monthly cost of drugs at CVS by \$10 led to 5-10% of people not filling their prescriptions, implying a high price elasticity. Such access questions can be even more severe for smaller subsets of the population, particularly disadvantaged or marginalized groups. For example, large

concentrations of prison inmates have Hepatitis C, but only around 1% of them have received treatment. On questions of equity, it was suggested that the savings from drug-price declines could be invested in wider public health initiatives, specifically things influencing the social determinants of health.

## Session 2

### Presentation from [Rena Conti](#) and [Josh Sharfstein](#)

Rena Conti of Boston University's Questrom School of Business summarized Louisiana's experiment for expanding access to a drug that cures Hepatitis C, a disease that is widespread among the state's Medicaid and prison inmate populations. Due to budget constraints, the state could not afford enough medication to treat the whole population. The solution, the governor and health secretary decided, was to try an alternative to the fixed-priced-per-pill model. The state offered the makers of the drugs—there are three—an approach that reflects the fact the marginal cost of producing each additional pill is very small. Dubbed a Netflix-style subscription model, the state asked the drug maker to offer a flat fee that would cover the drugs necessary to treat all of Louisiana's Medicaid and prison population over a five-year period. (Shortly after our conference, the state announced it would contract with Asegua Therapeutics Inc., a subsidiary of Gilead Sciences Inc., to provide the medicine, beginning July 1, 2019.) The presenters cited two reasons why Louisiana became a leader in this field. The first was that a high proportion of its population is infected with Hepatitis C. (It also has a very high HIV rate.) The second was the leadership demonstrated by the governor and the secretary of health, who viewed the state's Hepatitis C problem as a pressing public health challenge.

For the Medicaid population, the state is using the existing Medicaid supplemental rebate program. For the prison population, the state is making expanded use of the 340(b) programs, a federal program that provides discounts to hospitals and clinics that serve low-income or uninsured patients. Both had precedent, which was important politically, and neither threatened the Medicaid ["best price" rule](#), because manufacturers were not required to factor Medicaid pricing or purchasing entities with 340(b) status into their best price calculation. The state did not need to seek a waiver from the Centers for Medicare and Medicaid Services (CMS).

Conti viewed this as both an equity issue and an innovation issue. Pharmaceuticals receive government assistance for R&D through government grants and research cooperation. Such was the case for Gilead's Hepatitis C drug, Sovaldi, which was funded by NIH, as Anderson pointed out in his earlier presentation. But Conti suggested innovators receive a disproportionate amount of the windfall. Taxpayers indirectly support innovators through the tax system and should have access to the fruit of this innovation. What Louisiana has done is shift the discussion towards allowing everyone to gain access to public health.

Josh Sharfstein of the Johns Hopkins Bloomberg School of Public Health added that Louisiana conceptualized the problem as a public health challenge and not a drug pricing challenge. Hepatitis C is curable, but many do not have access to the necessary drugs. Sharfstein recounted [Peter Bach's conclusion](#) that it would be cheaper for the government to [buy Gilead](#) and make the drug accessible than to buy its products at market prices. Sharfstein suggested that Louisiana has found a path to address this public health challenge. He gave credit to the companies for participating, and said it reflects their recognition that people who can't afford medication can and should benefit from the fruits of innovation.

## General Discussion

Conti was asked whether the threat of the state invoking a century-old patent law, known as [Section 1498](#), was a lever to get the drug companies to the table. (Section 1498 allows the government to use what amounts to its power of eminent domain to circumvent patent protections, provided the patent holder is fairly compensated.) She replied that 1498 was not new; it has been on the table as an option for almost 100 years. And it remains part of the toolkit.

Louisiana's ability to avoid best price rules for Medicaid and its choice not to impose price controls were deemed particularly important. Participants agreed that this type of negotiation can be more difficult for private insurers because of Medicaid's best price rule, which requires that Medicaid be able to purchase drugs at the lowest price paid by any buyer. In a subscription model with an up-front payment and the rest paid for by rebate, Medicaid could claim that the best price is zero. Then every Medicaid program could demand the drug at zero costs, a possibility that obviously scares off drug makers. In other words, Medicaid's best price rule can rule interfere with value-based purchasing or innovation. Louisiana also avoided price controls, which can doom certain types of innovation or therapies in perpetuity. For example, the [Ryan White Program](#) with HIV drugs made sense at the time, but over time it prevented innovation in HIV drugs.

Another participant pointed to the challenge of pricing a new drug. Pharmaceutical manufacturers are in constant discussion with distributors. The ongoing challenge is that the sickest patients subsidize healthier ones. More discussion is needed around value-based insurance design and a patient's out-of-pocket cost. The question for a pharmaceutical company, however, is how to set a price relative to volume, or the potential patient population. For example, for treating cardiovascular disease for 5 million people, pharmaceutical companies would want to know the goals: do they want to treat everyone? If not, what percent? There is a lot of interest among pharmaceutical companies to do these types of deals, but the mechanics are difficult. The presenters agree that pharmaceutical companies face uncertainties when setting the price; thus they stress that leadership matters. In Louisiana's case, the state set the goal of treating Hepatitis C. Both sides (the state and the drug companies) had rights and responsibilities. If the pharmaceutical companies were willing to take part, then it was the state's responsibility to treat people. One participant noted that the public won't benefit if drug companies are successfully pressured into lowering prices, but the states neglect their responsibility to see that sick residents are treated. The presenters argued that replicating the Louisiana model elsewhere is possible. Another participant emphasized the importance of coordination and leadership, and asked what would bring pharmaceutical companies to the table.

States have the potential for innovation and authority in this area, but the infrastructure for establishing health policy is lacking in many states. The secretary of health and the head of the state Medicaid program are typically the only officials focused on public health issues. The solution is to build up the public infrastructure at the state and local level. The CMS State Innovations Model Initiative ([SIM](#)) was a breakthrough in giving resources to the states and in thinking about health policy at a local level. One participant pointed out that the problem may come back to pricing. Louisiana is a poor state that couldn't treat its people. This was clear to pharmaceutical companies. In a richer state where there is room for negotiation, would pharmaceutical companies be as willing to negotiate? Does that make replicability harder? Discussants answered that global companies have made different arrangements with different countries—and could do the same with different states.

Another issue in replicating the Louisiana approach is the difference between acute/infectious disease and chronic disease. For example, HIV drugs are usually not one single drug, but a cocktail of drugs that are taken forever by the patient. As a result, it would be difficult to coordinate with several manufacturers for drug purchases and pricing, especially if drug resistance develops among a patient and the cocktail needs to be modified. Additionally, budget constraints would be different for each participant. Although value-based insurance is proposed as a solution for the latter point, evidence around value-based insurance design experiments is mixed. Participants also commented that the subscription model is a move away from value-based pricing. Instead, it is a budget-based negotiation, which isn't a bad thing—but the two concepts are different, and talking about them together can be confusing.

Beyond Louisiana, participants discussed Washington state, which is implementing a similar program. Washington had a two-part bidding process instead of a unified process. One part focused on the Medicaid population, which was like Louisiana's model; the other part focused on the general population covered by the state, including state employees and the incarcerated. This looked like a standard volume discount approach. The discussants thought that the real innovation in Louisiana was in its implementation—Louisiana did not require waivers. It went through the process for Medicaid best price practices and leveraged [340\(b\)](#) capabilities. Washington did not do the same.

Presenters pointed out that the subscription model idea came from a two-part report from the National Academies of Medicine ([phase 1](#) and [phase 2](#)). Although the approach was unique, Australia experimented with a similar model, using budget caps. The government stated that it was spending \$1 billion on a drug, and companies were invited to help treat as many people as possible.

Discussants pointed out that coordination with the government is important. Both Washington and Louisiana worked closely with CMS. In fact, participants pointed out, Louisiana wanted a waiver originally, but CMS is limited what it can waive, according to [Section 1115](#). They said that obtaining a waiver is challenging, in general. Instead, Louisiana and Washington leveraged Medicaid's supplemental rebate program, which has been in place in almost every state for years, so the idea is not new. Following that path is a way for other states to replicate Louisiana's and Washington's models. The difficulties in replicating what Louisiana and Washington are doing, they pointed out, are problems with leadership and infrastructure.

## Session 3

Presentation from [Heidi Williams](#) on her paper, "[Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials](#)"

[Heidi Williams' slides](#)

Williams and her coauthors studied whether there is systematic underinvestment in longer-term research projects by looking at late-stage versus early-stage cancer treatments. The FDA generally requires that clinical trials showing a drug's effectiveness be completed prior to a drug being approved, creating long lags between invention and commercialization. This lag is particularly large for drugs treating forms of cancer with long survival times, since these need longer clinical trials to determine whether they are effective. Williams and coauthor argue that this requirement discourages firms from investing in longer-

term research, particularly in drugs, because these lags decrease the de facto exclusivity period for innovating firms.

Williams and coauthors developed a theoretical model whereby drug companies conduct research subject to cost constraints related to the patent exclusivity period, the commercialization lag, competition from generics, and various other factors relative to some social optimum. In the model, private firms systemically underinvest, both in terms of the level and composition, in R&D relative to the social optimum, particularly for projects with long commercialization lags.

To test their theory empirically, the authors looked at clinical trials for cancer treatments from 1973-2011 and patient survival data from 1973-2004, by cancer and patient types. They found that patient groups with higher survival rates had fewer clinical trials, a finding that implies that longer commercialization lags decrease R&D. To get at causality, Williams and coauthors also found that this relationship does not exist for types of cancers that use surrogate endpoints in drug trials. (A surrogate endpoint is a measure of a treatment's effectiveness—like a shrinking tumor, for example—that can be detected sooner and is a good proxy for an actual clinical endpoint, in this case the clinical endpoint being death.) In other words, types of cancers that allow for such endpoints and therefore have shorter commercialization lags do not have fewer clinical trials. This is particularly shown with hematologic cancers that have more surrogate endpoints for trials. The authors argued this is evidence that the fact that there is less R&D for types of cancers with longer survival rates is not the result of more difficulty in scientific discovery. In addition, they found that the negative correlation between survival times and R&D (measured by the number of clinical trials) is consistent both for public and private investment, but is larger for private firms than for the government. They explored various policy options in the paper and endorsed expanding the number of approved surrogate endpoints and providing targeted R&D subsidies for projects with longer commercialization lags.

## General Discussion

The conversation focused initially on [surrogate endpoints](#). In particular, Williams suggested that more surrogate endpoints be adopted to shorten the length of these trials, increase investment in longer-term disease drugs, and speed the rate at which new drugs get to market. There was discussion on the challenges and benefits of such an approach. For one, validation of surrogate endpoints is often difficult and requires a substantial amount of study. Some participants noted that knowledge of good surrogate endpoints and reliable biomarkers are often endogenous, in that they depend on existing knowledge of certain diseases and on pharmaceutical companies' investment in certain types of drug research. There was discussion of the [Framingham Heart Study](#) and its value, including information on relevant biomarkers and surrogate endpoints for cardiovascular disease. Some noted a desire to fund a new Framingham-type study but for Alzheimer's disease, in order to come up with new surrogate endpoints. Most agreed that this would be a powerful resource, but argued that it would be expensive, given that survey respondents would need to get medical imaging regularly throughout the course of the survey. It was noted that electronic health records may already have some of the data needed to do such research, particularly for data prior to [reforms](#) implemented in 2015. Others noted that research into biomarkers for Alzheimer's was already underway and could provide relevant hypotheses for such a study. For example, recent [research](#) looked at the buildup of brain plaque in Alzheimer's patients as a potential biomarker. Though this particular indicator had [not been widely adopted](#), existing research had only

looked at patients who had already developed brain plaque, rather than looking at patients before they began to develop plaque; in other words, research in this area seemed to still be preliminary. Others noted that certain biomarkers can be very drug-specific and hard to generalize for broad approval *ex ante*. While this may be true, the case was also made for more generalized indicators that aren't company-specific, and might provide sufficiently broad benefits to receive public research funding: for example, blood pressure as a biomarker for cardiovascular disease or tumor shrinkage for cancer.

Discussants also noted difficulty with regulation that may prevent companies from adopting surrogate endpoints in clinical trials. The FDA's Center for Drug Evaluation and Research sets [standards](#) for approval of new molecular entities. There was some critique that the CDER's approval of surrogate endpoints was nonsystematic, with many well-documented biomarkers underused and standards for others that were used ill-defined. It was noted that even if the bar for approval of surrogate endpoints was set high, there could still be significant value in providing clarity and certainty around the approval process. For example, the FDA said they would approve, at some point in the future, HPV incidences as an indicator for cervical cancer vaccines. Even though the action was not imminent, clarity around future policy shortened the length of trials and changed the cost profile of research for the drug, leading to new drugs being brought to market faster. In other scenarios, though, the approval process can be difficult, given the ambiguousness of trial results. Certain cases that don't involve thick tails in patient responses based on a small sample size make it difficult for the FDA to assess the validity of trials using surrogate endpoints. Some standards therefore seem in order. Others argued that even if such approvals were made, allowing drugs to come to market faster, pharmaceutical companies are often still expected to complete the clinical trials through to their endpoints, which is costly. This may be because other countries also have stricter international standards for surrogate endpoints than the U.S.

There was discussion of patent rights and drug exclusivity periods. Williams noted that her research showed, regardless of the overall length of patent exclusivity, investment in longer duration drug trials appears to be lower than investment in shorter duration drug trials for any given length of overall exclusivity. Therefore, some relative incentive to invest in one type of research relative to another is needed. The Hatch-Waxman Act, for example, includes provisions designed to provide relative incentives for different types of research by varying the length of [patent extensions](#) for different types of research. However, in practice all companies that applied for the extension got the same 5-year exclusivity extension, regardless of the type of research they were doing. This did not fix the shortfalls in financing for types of drugs trials relative to each other. An alternative option of offering lengthier patent rights for longer-term drugs from inception is illegal under WTO rules, making reforms difficult. It might be possible to get around the rule by offering different exclusivity terms rather than different patent terms, but nothing in the space has been attempted so far. There was discussion of delaying patent publications until drugs were actually approved, since pharmaceuticals is one of the few industries where firms can't sell drugs for which they have patents while they wait for FDA approval. There was some pushback against this idea, though, as a change in the rule could cause distortions in other markets, such as technology. So-called '[submarine patents](#),' instances where there is a long delay in the publication of a patent from the date of issuance, have caused problems in the past where they led to major disruptions for competitors who had been using the patent technology prior to when the patent 'surfaced.' There was also warning against extending patent exclusivity length, as the current 12-year system was designed to recoup the cost of investment and not provide additional rents, and the FTC regularly litigates against firms abusing the system.

Overall, there was significant support for the paper’s use of systematic empirical methodology to study incentives. In particular, it was noted that the research proves that incentives for investment in drug R&D are not some unknowable or unmeasurable phenomena but can be studied with detailed empirical analysis. While Williams acknowledged that the observational nature of the data used in the research did not prove anything definitively, the intent was to rigorously test an economic theory with data to inform the debate.



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