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> If you put the federal government in charge of the Sahara Desert, in 5 years there'd be a shortage of sand.
>
> Milton Friedman
> *Nobel Prize-winning economist*

Introduction

Drug pricing and patient affordability of medicines have been major political issues in the 2016 US presidential election. Calls for the government imposition of price controls on the pricing of older generic drugs,[1] limits on patient out-of-pocket drug expenses,[2] and in general more limits on pharmaceutical pricing have been major policy positions by candidates. The drug industry has been cast in a very negative light during this political cycle. Not surprisingly, the Pharmaceutical Research and Manufacturer of America (PhRMA) stated Mrs. Clinton's plan would "turn back the clock on medical innovation" while further noting restricting patient access to medicines.[2] Some health economists have expressed skepticism over Mrs. Clinton's plan as creating unintended adverse effects that run against promoting true innovation with little effect on stemming drug prices.[2] The issue of high drug costs is also a hot topic in the medical literature among healthcare professionals, especially given the growth of personalized medicines geared toward targeted therapies in areas such as cancer (a sample of such articles are referenced).[3-9] The high cost of cancer medications has caused oncologists to reevaluate the value framework for these drugs.[10]

No long-term "solution" on drug pricing has emerged gaining broad consensus among public policy officials and politicians, patient advocacy groups, medical and health service researchers, and healthcare professionals. However, the "quick and easy fix" option of price controls invariably comes up. While this option is publicly appealing, the question is what (if any) unintended effects might occur from enacting drug price controls? This white paper will review the evidence on the relationship between drug price controls and patient health outcomes, especially given the importance of the pharmaceutical industry and drug innovation to the overall social well-being of society.

The imposition of drug price controls according to microeconomic theory is hypothesized to affect patient health outcomes in two ways:

1. Price controls diminish the diffusion of new drug technology that can be used by patients. Assuming overall new drug technology advances patient health, the result would be eventual lower health outcomes.
2. Price controls decrease incentives for pharma industry investments in R&D, decreases drug innovation output, which in turn results in eventual lower health outcomes.

The effects outlined in the first relationships are relatively short-term, whereas the second relationships are seen over the long-term given the typical length of the total R&D

process to bring a drug to market being 10-12 years. What does the published evidence say on the above relationships?

Price Controls and the Diffusion of New Drug Technology

There is strong evidence on the relationship between differential pricing by country and diffusion of new drug technology. IMS Institute for Healthcare Informatics has provided forecast evidence that "in 2020 the use of new medicines, introduced in the prior 10 years, will represent 0.1% of volumes in pharmerging markets, compared to 2-3% in developed markets."[11] While this difference in drug utilization is likely the result from a combination of both relative price and income effects across markets, nevertheless, pharma companies will seek diffusion of new drug technology in countries where they can reap higher prices to pay for higher R&D costs.[12-13] Empirical research has shown the shift in pharma R&D drug portfolios has been driven in part by greater flexibility on drug pricing available to companies and less price competition from generics in the launching of specialty medicines.[14]

Prior academic empirical research has shown price controls having a statistically important effect on the extent and timing of the diffusion of new drug launches by country. Companies choose to avoid countries in Europe with lower prices caused by stringent price controls, and introduce less new drugs after entering a price-controlled market.[15] The existence of parallel imports further delays new product launches, meaning that price control policies in one country can have spillover effects into other countries.[15] Another large study across 15 countries found negative new drug price elasticities in the -0.75 to -1.1 range and cross-price new drug quantity effects with respect to old drug pricing being positive but small in effects.[16] This study is unique in also capturing the effects of detailing promotion by specific case study therapy classes across the sample countries.[16] They found promotion on older drugs negatively affected new drug share.[16] Another large study done for 642 new drugs in 76 countries from 1983-2002 found robust strong findings on patent and price regulation effects on the diffusion of new drugs in the manner predicted by economic theory.[17] Lastly, another large study done over time and across selected OECD (Organization for Economic

Cooperation and Development) countries found that higher US brand prices relative to other countries contributed to faster uptake of new drugs but also higher spending per capita on prescription drugs.[18] Thus, overall, the literature here finds what economics 101 teaches us - incentives do matter. What about the more complicated relationship, do price controls affect patient health outcomes, through the effect on reductions in pharmaceutical R&D?

Price Controls and Patient Health Outcomes

The relationship between price controls and patient health outcomes is more indirect and requires a chain of effects to occur. The first chain to be assessed is the relationship between drug pricing / price controls and pharma R&D investment. The second chain is the relationship between the growth of R&D drug innovation and patient health outcomes. There is a long line of research that establishes the first part of this relationship, the connection between drug pricing and price controls to changes in pharma R&D investment. Why is this connection so important as the pharma industry landscape is evolving? The growing shift in pharma R&D focus on specialty medicines and especially those that are classified as orphan drugs[19] require higher incentives to compensate for the added costs and risks involved with large molecule / biologic-based drug technology.[20] Evidence on the impact of the Orphan Drug Act of 1983 in the US affirm that the incentives enacted through this legislation has generated the intended policy effect of increasing the number of drugs developed to treat rare diseases (more than 500 drugs since the act passed in the US alone, with other countries adopting similar orphan drug programs).[21] Numerous empirical studies show a strong connection between the enactment of price controls and reductions in pharmaceutical R&D investment, thereby leading to decreases in new drug innovation.[22-23] Another study estimated an elasticity whereby a 10% *decrease* in the growth of real drug prices affected an approximate 6% *decrease* in the growth of R&D intensity.[24] A recent study concluded that the enactment of patents and exclusivity provisions, while having pros and cons (e.g., the establishment of monopoly drug pricing) as a policy approach, would still play a dominant role in providing the necessary incentives to encourage biopharmaceutical R&D.[25] Overall,

there is an established body of academic literature that establishes the relationship between drug pricing and price controls to pharma R&D investment and drug innovation.

What about the second relationship chain on the adverse effects of R&D development and drug innovation from constraints on patient health outcomes? Here too, there has been empirical evidence provided in the literature. The most direct study is one that estimated the effect of real (inflation-adjusted) price declines from price controls to reductions in R&D investment, and then in turn, on life-years lost (in millions).[26] Model estimates determined that a -10% (-30%) [-50%] decrease in real drug prices from price controls respectively decrease R&D investment by -5.8% (-17.5%) [-29.2%], which in turn, affect life-years lost (in millions) respectively by -40.1 (-113.5) [-178.8].[26] This connection to reductions in life-years lost depends on the relationship that decreases in the diffusion and utilization of new drug innovation affects patient health. However, here too is empirical evidence. Pharmaceutical innovation was estimated to increase life expectancy by 1.27 years during the period 2000-2009 for 30 developing and high-income countries.[27] Similar studies have been conducted by the author showing increases in country life expectancy from pharmaceutical innovation. Not all empirical studies show a strong relationship between pharmaceutical spending and life expectancy, such as one done on Canada that found no effect on drug spending affecting infant mortality and life expectancy at 65.[28] Economic theory may provide a theoretical structure to explain how less pharmaceutical R&D and lower diffusion of drug innovation would result in lower health outcomes. However, the empirical challenges of determining a robust effect amongst all the other factors that can affect life expectancy and/or health outcomes outside of the diffusion of pharmaceutical innovation is a daunting task. While the empirical studies presented here overall generally show a strong relationship in price controls affecting patient health outcomes, more research is likely needed to determine the robustness of the effect and its magnitude.

Will Direct Drug Price Controls be Enacted in the US?

This final section will briefly explore the possibility that despite the previous evidence presented, will direct drug price controls be enacted in the US? Despite public calls for price controls, there already exists numerous powerful mechanisms exerted by the government and market forces in controlling prices. For example, the federal government establishes Medicaid drug pricing based on significant discounts from the best commercial price being offered. Significant market forces affect pricing from increased branded drug competition, and competition from generic entry post-patent expiration (including early patent challenges) from bioequivalent and therapeutic drug substitution. Concentrated market power is shown to affect drug pricing and utilization by drug wholesalers, large health payers, and dominant pharmacy benefit managers. What is also unchallenged is the recognition of an industry undergoing rapid fundamental changes. More, not less incentives, will be needed for pharma companies to unlock the solutions to address unmet medical needs caused by very challenging diseases. The easy disease targets using traditional small molecule drugs are rapidly vanishing. Opportunities are very limited to capitalize "low hanging fruit" by drug companies. Complicating the challenge facing drug companies is that both improvements in health outcomes *and* costs of care will be measuring sticks to determine future rewards from drug innovation. This will be an expensive endeavor, and questions exist, as written in previous white papers published here, whether society is willing and able to pay for increases in drug innovation needed to solve these medical challenges. The future is admittedly uncertain.

Various groups have traditionally banded together to advocate against imposing direct drug price controls in the US.[29] However, while their efforts have been historically successful to avoid this step, that coalition is showing signs that maybe the current environment and escalation of drug costs is weakening the resolve to work against price controls.[29] The dramatic increases in prices necessary to support drug innovation are straining that coalition, while the current commercial model that companies are using to sustain profitability mainly through price increases is clearly unsustainable in the long run.[30-31] As reported in this white paper series, increasingly, new drugs are being priced beyond the means for payers (both government and commercial plans) to support and ordinary patients to access and afford. Even for drugs that deliver both extraordinary health outcomes and cost-effectiveness (like drugs that cure

Hepatitis C that prevent costly complications due to the disease), the cost of these drugs limit their diffusion to the many more who could benefit from them. There are other similar examples of new drug innovation. Adoption of these novel drugs would bankrupt healthcare reimbursement systems if everyone received such therapies. The backlash by the public to demand that such drugs be more widely available is causing a complete reevaluation of the system that determines drug pricing, of which, imposing drug price controls is increasingly deemed as part of that solution.

What is also becoming clearer, as presented here in this white paper series, is that the commercial model pharma companies are employing to generate and support current drug prices of these specialty medicines require a reevaluation and radical change in their approach. The shift to focus on specialty medicines means the current commercial model, based on a set of increasingly obsolete market dynamics and less-emphasized drug technology going forward, are vanishing and will need to be changed.

Companies need to be focusing and demonstrating in *everything they do* along the entire project/product life-cycle on improvements from new drug innovation in producing better health outcomes and costs of care. The backlash against drug pricing and greater calls for price controls is a likely reflection that the industry has not yet effectively delivered this outcome/value-based argument. The good news for the industry is that there is still some time available for needed internal changes to better make this argument. If, however, changes are not made, the growing politicalization of drug pricing and public discontentment will likely mean even greater government involvement, and with it, even more onerous effects as exemplified in the opening quote. The empirical evidence presented here suggests that a more heavy-handed approach by the government to erect price controls will not promote overall social well-being, decrease needed drug innovation to address significant unmet medical needs, and adversely affect patient health outcomes.

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