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Incentives for pharmaceutical innovation: What's working, what's lacking

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ABSTRACT

This article provides an overview of the performance of innovation policies in the pharmaceutical sector. It discusses the conditions under which various policies are mostly likely to result in socially valuable R&D. Interactions between different domestic policies, as well as the importance of considering strategic interactions between governments, are also highlighted.

1. Introduction

The Covid pandemic has brought increased attention to the pharmaceutical sector, and in particular to the development and distribution of vaccines and treatments. Health care's increasing share of OECD economies and the growth in health care spending driven by patented pharmaceutical treatments has long been a concern to policymakers.

Much of the increased life expectancy realized during the 20th and 21st centuries can be credited to pharmaceutical interventions. Pharmaceuticals are easily transported and adopted around the world, and usually simple to deliver to patients: that is, the diffusion of innovation is broader and faster than is the case for many other medical breakthroughs, such as surgical treatments. Production costs, while higher for biologics and vaccines than for small molecule drugs, are generally low. The burden of infectious diseases has fallen dramatically. In the last 20 years, for example, a recent study in the United Kingdom found that the introduction of new vaccines for human papillomavirus "has successfully almost eliminated cervical cancer" (Falcaro, 2021); the World Health Assembly has targeted the elimination of viral hepatitis due to the availability of oral direct-acting antiviral treatments (World Health Organization, 2016); and CFTR modulators are expected to have dramatic effects on life expectancy for those with cystic fibrosis (Balfour-Lynn and King, 2020). Pharmaceuticals are used to manage HIV, diabetes, and many chronic cardiovascular conditions. The rapid development of vaccines for Covid is credited with preventing the deaths of almost half a million lives for people over 60 in Europe alone, less than one year after their introduction.

However, in addition to concerns about inequitable access to pharmaceutical innovations and their affordability, policymakers worry that current innovation policies provide insufficient incentives to develop, e.g., novel antibiotics or treatments for diseases that primarily affect less developed countries. Some argue that pharmaceutical firms produce too many "me-too" drugs, offering little clinical benefit over existing treatments. These concerns and others have led various stakeholders to call for changes to innovation policy. One prominent recent example is the proposed patent waiver for Covid vaccines, now being considered by the World Trade Organization. Others have gone further, arguing that research and development should be "delinked" from prices (Love, 2011), or that pharmaceutical production should be nationalized

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(Mazzucato et al., 2020). Others push for expansion of existing policies, such as more public financial support for medical research. US President Biden's proposed budget for 2022 includes an increase of 10% and 25% on basic and applied research, respectively, for the Department of Health and Human Services.[1]. The US Trade Representative has maintained its position on the importance of intellectual property (IP), and the implementation and enforcement of IP laws by trading partners.[2]

In this paper, I provide an overview of the success and failures of innovation policy in pharmaceuticals. I focus on the underlying conditions necessary for different innovation policies to be effective at directing innovative effort towards targets where the social return is high.

2. Innovation policies in pharma

Innovation policy plays an especially important role in pharmaceuticals due to the nature of drug development. Because the process of identifying and testing a potential treatment is long and expensive, with high failure rates and easy imitation ex-post, the private sector has little incentive to invest in the absence of policy interventions. These can either "pull" innovation in from the private sector by increasing expected profits, or "push" innovation out from the public sector by underwriting the costs. The former include patents and other forms of exclusivity as well as prizes and advance market commitments. Grants, subsidies, and tax credits are examples of push approaches. Both play important roles in pharmaceutical innovation and have different champions.

2.1. Push versus pull

A key difference between push and pull is how information is aggregated. Pull policies rely on "the market" to a greater extent, in order to identify where demand or need is highest and what firms or researchers are best positioned to pursue an innovation. In contrast, most push policies rely on elected officials and expert committees to determine how much funding should be allocated, to what diseases, and to which researchers. Information asymmetries around the value of a particular project and whether money is spent effectively introduce a number of agency issues for either shareholders or government funders. The relative performance of various innovation policies, not surprisingly, depends on whether downstream product markets for the output – pharmaceutical treatments – are efficient, or whether government funders are efficient in aggregating information and allocating funding accordingly.

An additional consideration is the availability of capital to finance innovation. As mentioned above, pharmaceutical development has high failure rates. Who bears the risk of failure also differs between push and pull policies, with shareholders generally incurring the costs under a pull policy and government funders under a push policy.

2.2. Indirect policies

While IP and grants are explicitly intended to promote innovation, they are hardly the only government policies that influence the level and direction of R&D. Indeed, innovation is potentially affected by any policy that affects expected profits or the key underlying conditions for push and pull policies, discussed in the sections that follow.

For pharmaceuticals, a number of health policies are clearly relevant. Regulations on entry (i.e., the standards for clinical trials necessary to establish safety and efficacy to an agency's satisfaction) affect the cost of bringing a drug to market, estimated to exceed $2.5 billion (DiMasi et al., 2016). Regulations on price affect revenues, as well as entry strategies (Kyle, 2007). As both costs and revenues directly enter into a firm's expected profits, changes to either would likely have some effect on innovative investment. Coverage mandates or expansion of insurance affect the potential market size for a pharmaceutical innovation, which can pull innovation in the direction of those populations or treatments affected (Finkelstein, 2004; Blume-Kohout and Sood, 2013).

Policies around the provision of information – either about relative prices or about quality – may also be important, and may depend on whether the patient or the physician receives the information (Branstetter et al., 2016). For example, Sorensen (2000) concludes that patterns in price dispersion of pharmaceuticals across pharmacies are consistent with heterogeneous incentives for consumer search. Epstein and Ketcham (2014) find that physicians adjust their prescribing in response to information about a drug's cost to a patient, and Ching and Ishihara (2012) conclude that marketing of drugs to physicians plays an important informative role. However, there is also evidence that doctors have sticky prescribing habits (Datta and Dave, 2017), despite the frequency with which medical reversals occur (Prasad et al., 2013). Kyle and Williams (2017) find slower adoption of drugs with better scores for therapeutic added value in the US compared to other developed countries, which may suggest either insufficient information about quality or insufficient incentives to respond to it.

More subtle effects on innovation, both in terms of theory and empirical results, may arise from competition policy. For example, rules concerning horizontal cooperation in R&D must balance potentially pro-competitive effects on innovation against the possibility of anti-competitive behavior downstream. Agreements arising from patent disputes, such as those

[1] Proposed budget for 2022

[2] US Trade Representative 2021 Trade Policy Agenda and 2020 Annual Report

between originator firms and generic producers, can raise competition concerns as well: in addition to the direct effect on product market competition in the short run, the period of time an originator expects to benefit from exclusivity (which can be specified in such agreements) also has consequences for investment incentives (Li et al., 2021).[3] Innovation is increasingly considered by competition authorities in evaluating mergers and acquisitions. There is some empirical support for a comparative advantage of large firms in drug development, through economies of scale and scope (Cockburn and Henderson, 2001) or better internal capital allocation to projects (Guedj and Scharfstein, 2004). However, recent work has highlighted the risk of reduced innovation as a result of "killer acquisitions" (Cunningham et al., 2021).

Trade policy can also be important for innovation incentives. Trade agreements change the potential market an innovator may access, which in turn affects the incentives to invest. Trade is also a channel for learning by importing or exporting, as well as technology transfer through foreign direct investment (see Kiriyama, 2012 for a useful summary of these mechanisms and their empirical support).

In recent decades, intellectual property (IP) is often a key component of multilateral and bilateral trade agreements. These agreements have generally increased patent protection for pharmaceuticals, and may provide further protection by specifying minimum data exclusivity terms or requiring patent linkage. Kyle and McGahan (2012) finds that the expansion of patent protection did cause an increase in innovative efforts in pharmaceuticals, using disease-level variation in market size across countries.

Another aspect of trade policy concerns the exhaustion of IP, or the tolerance of so-called "parallel trade" in IP-protected products. If the owner of the IP cannot rely on IP to block the trade because the IP is exhausted, arbitrage of price differences is likely to occur. Parallel trade is common in the European Union, and members of both political parties in the US have proposed allowing imports from Canada and other countries as a means to lower US drug prices. Such policies may fail in this particular objective (Kyle et al., 2008; Kyle, 2011; Dubois and Sæthre, 2020). The consequences for innovation have not been empirically tested, though theoretical models generally predict negative effects depending on the relative size and similarity of trading partners (Bennato and Valletti, 2014; Reisinger et al., 2019).

3. When are patents effective?

Patent protection and other forms of intellectual property play a bigger role in pharmaceutical innovation than for perhaps any other sector (Levin et al., 1987). As is well understood, these policies should balance the dynamic incentives for innovation that result from shielding an innovator from competition, thus allowing him to appropriate some of the benefits, against the static costs of higher prices and/or reduced access.

A large body of empirical evidence confirms that R&D effort responds to expected profits. At least in developed markets, expansion of market size in the presence of patent protection is associated with increased investment and treatments. Both Acemoglu and Linn (2004) and de Mouzon et al. (2015) use exogenous changes in the age distribution of the population to identify the effect of market size on the number of new treatments developed. In an example of how health policy can shape innovation incentives, Finkelstein (2004) shows that vaccine mandates led to increased development of new vaccines.

Empirical assessments of patent policies more specifically generally find that R&D effort responds to additional protection or exclusivity in rich countries. A recent example is (Gaessler and Wagner, 2020), who show that firms are more likely to abandon clinical development when a project's expected market exclusivity falls. Gilchrist (2016) shows a more subtle effect of exclusivity on innovation incentives. He finds that when the first entrant in a disease class has longer exclusivity, more follow-on drugs are introduced. The introduction of patent protection for pharmaceuticals is also associated with increases in domestic innovation (Qian, 2007) and as well as greater R&D effort directed at diseases that see an increase in the size of the patent-protected market (Kyle and McGahan, 2012).

Market exclusivity policies can also be used to encourage innovation in specific disease areas. One such example is the additional exclusivity granted to so-called orphan drugs, those that treat diseases with very small numbers of patients. As summarized by Sarpatwari et al. (2018), orphan drugs comprise an increasing share of new drugs launched. An interesting twist to exclusivity policies is the Priority Review Voucher, proposed by Ridley et al. (2006) and adopted in 2007 in the US, which provides drug developers a tradeable voucher to speed up the review of a new drug application at the FDA (which in practice extends the market exclusivity of a product, as it reaches the market earlier). These vouchers are granted to firms that have developed products for a neglected tropical disease, though they can be used for any product. Between 2007 and 2019, 31 such vouchers were awarded.[4]

Despite evidence that patent policies pull innovation, not all such innovation is valuable. To be effective at pulling innovation towards efforts that are socially valuable, the profits derived from patents must be linked to social value. That is, if we believe that curing cancer yields larger welfare benefits than curing baldness, then the profits associated from curing cancer must also be higher with a patent system. I next consider what conditions are required for this outcome.

[3] See also Panattoni (2011); Gilchrist (2016), and ?, among others, for a discussion of the interplay between patent challenges and investment incentives.
[4] See GAO summary.

3.1. Functioning of product markets

While the market power that results from patent protection obviously implies that the downstream market for a patented drug is not perfectly competitive, that market still needs to function well in general. By this, I mean that stakeholders have full information about a drug's quality; the price for a drug (or the revenues realized by innovators) reflects its quality; that insurance markets exist where patients might otherwise have limited ability to pay for the treatment; and that agency problems between physicians, patients, and third-party payers are of limited severity. Unfortunately, markets in healthcare are known to have many problems.

3.1.1. Agency problems

The lack of insurance in most developing countries contributes to the underinvestment in "neglected" diseases: though the social value of treating them may be high, the ability to pay is low. The same is true of treating many diseases in rich countries, but despite the potential for adverse selection, most developed countries have either public or private health insurance that facilitates access to at least a subset of pharmaceutical treatments. By more closely aligning profits with social value, health insurance complements patent policies to pull innovation towards treatments with high demand.

Of course, insurance introduces other distortions. When patients do not face the true price of a treatment, moral hazard may lead to overconsumption. Danzon and Pauly (2002) find that this moral hazard contributed to as much as one-half of the growth in spending on pharmaceuticals between 1987 and 1996. In a very different setting, Cohen et al. (2015) show that a generous subsidy to patients for malaria treatment resulted in greater use by patients *without* malaria. Unfortunately, addressing this moral hazard through the use of patient co-payments or cost-sharing risks distorting consumption as well (Manning et al., 1987). Nevertheless, its use has been increasing in the US (Baicker and Goldman, 2011) and in Europe (Drummond and Towse, 2012).

Agency problems at the patient level arise for reasons other than insurance as well. Some pharmaceutical treatments generate externalities. For vaccines, the positive externality that leads to underconsumption in the absence of some other policy intervention (Geoffard and Philipson, 1997). For antibiotics, the externality is negative: an individual's consumption of an antibiotic, particularly when it is not medically appropriate, contributes to antimicrobial resistance and diminishes the efficacy of treatments in the future. Unfortunately, patient demand – and the pressure a patient puts on the prescriber – is an important factor (Macfarlane et al., 1997; Bennett et al., 2015).

While we worry about the inefficiencies and health consequences of patients overconsuming ineffective treatments, or underconsuming effective ones, another concern is that the consumption patterns resulting from agency problems may distort innovation incentives. In the case of antibiotics, the interaction of patient agency issues with other policies has contributed to the decline in development of new treatments. In an effort to combat resistance, many health systems have introduced stewardship programs or similar efforts to restrict the use of novel antibiotics to which resistance is low. However, those efforts reduce the expected profits for a developer facing a limited term of patent protection or market exclusivity. Because profits are not linked to social value, the current approach to innovation has not pulled R&D in the desired direction, despite legislative efforts to address the problem through increased exclusivity (Darrow and Kesselheim, 2020).

The relationship between the patient and the physician is another source of agency problems. Because physicians are assumed to be better informed about the quality and appropriate use of a drug, most pharmaceuticals are accessible only if a doctor writes a prescription. However, the physician's interest may be imperfectly aligned with the patient's.

One obvious potential conflict arises if physicians directly profit from the drugs they prescribe. Western countries generally separate prescribing and dispensing (selling the drug) in order to avoid this. In Japan, where physicians can sell drugs directly to patients, Iizuka (2007) finds that physicians' prescribing is influenced by the markups they realize, but that they nevertheless are more sensitive to the out-of-pocket costs faced by their patients. In the US, where oncologists may dispense drugs administered in their offices, Jacobson et al. (2010) also find evidence that physicians respond to financial incentives.

Another concern is the influence of marketing or payments from industry on physician prescribing, even if physicians have no direct financial stake. In particular, if advertising leads to overprescribing in general, or excessive prescribing of less clinically appropriate drugs, or a reluctance to switch to less expensive generics, both consumption and investment incentives may be distorted. While I am not aware of studies that have examined this explicitly, many critics of the pharmaceutical industry point to its higher spending on marketing than on R&D. Perhaps agency problems change the relative return on marketing versus R&D. Marketing could also inefficient increase the rents realized on older drugs, depressing incentives to develop new ones.

The structure of the health insurance market may also influence expected profits, and therefore innovation incentives. Where private insurance plays a larger role, insurers may refuse coverage of treatments with long-run benefits (realized when the patient is no longer covered by the insurer), or with non-health benefits, or with unmeasured benefits. Prior to the minimum coverage requirements specified by the Affordable Care Act (ACA), for example, private insurers in the US were less generous in covering HPV vaccines, leading to low take-up (Hawkins et al., 2021).

In countries where insurance is largely provided by government (i.e., most developed countries), governments can act as monopsonistic purchasers of pharmaceuticals. This creates the opportunity for hold-up of producers, who have already sunk R&D costs, and lead to underinvestment. Tight budget constraints are likely to exacerbate this problem, as the costs of procuring pharmaceuticals are visible and realized in the short term, while benefits may be more difficult to measure and realized over a longer time horizon. Recent examples of this tension include direct acting retroviral treatments for Hepatitis

C, which have cure rates above 95%. Despite very high price tags, health technology assessments generally conclude that these products are cost-effective. However, the budgetary challenge they present has led to efforts to limit their use. For instance, the National Health Service in the UK capped the number of patients who could be treated with DAAs in 2016, and Medicaid criteria for many states in the US restrict their use to patients whose liver disease is relatively advanced. The result is that drug developers may face greater incentives to develop products that are consumed at relatively low prices, but over a patient's lifetime, rather than products that have high upfront costs for curing a disease. This is similar to the potential for underinvestment in preventive care and vaccines discussed by, e.g., Dranove (1998) and Xue and Ouellette (2020).

3.1.2. Other information problems

Kremer and Snyder (2015) show that even without the agency problems just described, incentives for drug development may be tilted in favor of treatments rather than preventatives, or drugs over vaccines. This distortion arises if disease risk is heterogeneous and the seller of a preventative either does not know an individual's risk or cannot price discriminate across patients with different risk. In this case, the manufacturer is unable to extract as much surplus with a preventative as with a treatment sold once a patient's disease state is realized.

Imperfect information about quality can also complicate pricing or reimbursement decisions by payers, in addition to prescribing decisions by physicians. Increasingly, payers turn to health technology assessments (HTAs), which often compare new treatments to existing ones and/or estimate cost-effectiveness. Perhaps unsurprisingly, given the challenges in measurement and differences across stakeholders in the value placed on various product characteristics, there can be variations in these assessments (Nicod, 2017). In addition, cost-effectiveness tools may not always favor the adoption of efficient treatments because the measure of cost used an input reflects not the true cost of production, but the price faced by the payer (Jena and Philipson, 2009).

HTAs are usually conducted when a product is first introduced. Because clinical evidence about a drug's effects takes time to develop and diffuse, the "best" products (to the extent this can be measured ex post) may not realize the highest profits, which depresses incentives to develop effective treatments. Kyle (2018) shows that the grade for added therapeutic value assigned by the French health authority bears little relationship to the revenues realized. This suggests either that the HTA provides little information about quality, if one believes product markets work efficiently, or provides evidence that product markets in fact do not work efficiently. Interestingly, adoption of drugs that received the best scores were adopted more slowly in the US (Kyle and Williams, 2017).

Other empirical work has shown that physicians may be uninformed about quality as well as relative prices. For example, Cutler et al. (2019) estimate that a significant portion of Medicare spending is associated with "physician beliefs unsupported by clinical evidence." Azoulay (2002) finds that physicians respond to scientific evidence, but that marketing (itself influenced by this evidence) has greater influence. Using technology to inform physicians about prices, or more specifically, the out-of-pocket costs faced by their patients, can change their prescribing (Epstein and Ketcham, 2014). However, Carrera et al. (2018) find that this adjustment is small in the absence of a large, dramatic price difference.

Information about quality and prices can be costly to produce. Quality, especially, may be challenging to measure; clinical trials to yield reliable information are often expensive to conduct. Because this information is a public good, incentives to provide it may be too low; where it exists, physicians may not respond to it. As a consequence, the relative payoff of developing a breakthrough innovation versus a "me-too" may be distorted.

These factors contribute to the more nuanced policy effects identified in several empirical papers. The introduction of patent protection in developing countries did not induce greater investment in treatments for neglected diseases (Kyle and McGahan, 2012); developing countries have limited health insurance available and low ability to pay, so treatments without a significant market potential in richer countries remain unprofitable, even with patents. While the number of orphan drugs introduced has increased, Sarpatwari et al. (2018) suggest incentives to develop many orphan drugs may have been sufficient without such policies: in some cases, the orphan exclusivity expires before the relevant patents, and others face no competition even when patents and exclusivity have expired. Rather, the willingness of payers to accept very high prices may have provided the pull. Or, as shown by Yin (2008), some of these orphan introductions are the result of "salami slicing" – developers creating very narrow disease classifications in order to receive orphan designation, but expanding the use to wider markets after introduction. Expansion of health insurance in the US also does not seem to have pulled in pharmaceutical innovation, and one explanation offered by Garthwaite et al. (2021) is that the drug prices paid by Medicaid (which accounted for most of the expansion in coverage) are relatively low.

To summarize, patents do pull innovative efforts to a large degree. Situations in which they do not, or in which effort may be distorted, are often the consequence of a market failure downstream. While information problems pervade health markets, there is nevertheless some scope for improving innovation incentives by recognizing how other policies or regulations may interact with patent policies. A number of papers find that the quality of patent-induced innovation may be questionable, if measured at all (Finkelstein, 2004; Gilchrist, 2016; Yin, 2008). Because patent policy is a blunt instrument, in that it does not generally distinguish between major and minor innovations or evaluate therapeutic benefits, it is vital that the downstream market do so through price or market share.

3.1.3. Other limits of patents

As policy instruments, patents have a number of inherent shortcomings or limitations. Some are linked to the "one size fits all" nature of patents – a fixed term of 20 years from the date of application, the same for all technologies, and unrelated

to the importance of an innovation once an examiner determines that its inventive step meets the minimum threshold. This can be especially important in pharmaceuticals, because the patent clock begins ticking well before a product reaches the market. Budish et al. (2015) show that the fixed term of protection offered by patents penalizes innovative efforts that require longer development periods.

To some degree, patent term extensions such as those offered by supplementary protection certificates in the European Union or the Hatch-Waxman Act in the US can rebalance incentives. Another tool is exclusivity whose term begins when a product is launched, rather than from the time of a patent application (Eisenberg, 2012). Many countries use exclusivity terms in combination with the patent system, although there is little effort to tie the length to the quality of a new drug despite having more information about its therapeutic value at launch.

Another concern with patents is their effect on cumulative or follow-on innovation. The fact that a "me-too" drug receives the same 20 year term as a breakthrough product favors follow-on development efforts, some of which may offer clinical advantages or increase price competition. However, if follow-on research requires a license from patentholders, patents have the potential to block cumulative work.

The empirical evidence on this point is mixed. In a study covering all patent areas, not just pharmaceuticals, Galasso and Schankerman (2014) find that while patents appeared to have negative effectives on cumulative innovation in technologies like electronics and medical equipment, drugs were the exception. The entry of gene patents into the public domain was associated with an increase in follow-on R&D (Williams, 2013), but more recent work by Sampat and Williams (2019) conclude that patents on the human genome had no qualitatively important impact on cumulative research. The potential for reduced cumulative innovation may be more pronounced if broad patents are granted on new advances such as CRISPR or mRNA technology.

It is common to see multiple patents associated with a single drug. Because many patents are filed years after development first began, each offering an additional term of 20 years, this raises concerns about patent thickets and "evergreening," or extending the realized period of market exclusivity. While the primary concern is the static inefficiency that results from delayed or reduced generic entry (Hemphill and Sampat, 2012; Gupta, 2020), there may also be implications for innovation. First, it is not clear that products protected by multiple patents and that enjoy longer terms of market exclusivity are always the most important or the most therapeutically valuable, particularly if commercial value (which drives firms to file multiple patents) is not closely associated with therapeutic value. Second, even when therapeutic value and realized exclusivity are linked, the optimal exclusivity term is not infinite: producers of incumbent drugs still need incentive to develop new therapies, rather than continue to profit from old ones beyond some point. This balance may not be achieved in the present system.

3.2. Pull incentives beyond patents

The limitations of patents as pull mechanisms, as well as concerns about their effects on access to innovation, have generated many critics of the patent system. Boldrin and Levine (2013) famously argue that "there is no empirical evidence that they serve to increase innovation and productivity." The authors point to a "drought" in pharmaceutical innovation as evidence that the patent system has failed; in the years since the publication of their paper, the number of new molecular entities or biologics approved by the FDA has increased from an average of 25 per year from 2000 to 2013, to more than 38 per year from 2014 to 2020. However, other critics (e.g., Love, 2011) take issue with the direction of this innovative effort, noting that there are insufficient incentives to develop treatments that benefit those with low ability to pay.

Michael Kremer and co-authors have been especially important in designing alternative mechanisms for pulling pharmaceutical innovations. These include patent buyouts (Kremer, 1998) and advance market commitments (AMCs) (Kremer and Glennerster, 2004). These ideas underpin the AMC for pneumococcal vaccines, the Longitude Price, and the proposed Medical Innovation Prize Fund.

AMCs and prizes are appealing alternatives to patents where the latter clearly fail, such as neglected diseases. In addition to directing innovation where social value is high, a prize or AMC can avoid the problems of limited access due to high prices. Unlike the funding of innovation through grants, discussed in the following section, an innovation prize is only paid when an R&D effort is successful. This is an advantage if funders are risk averse, or face political consequences from having paid for failure.

However, as Kremer et al. (2020) explain, the design of AMCs is not straightforward. An AMC program must deal with information asymmetries viz-a-viz manufacturers and the potential beneficiaries; consider whether to focus on technologically close targets, or those that are distant; choose how many firms to which tenders should be allocated; etc. And, of course, there must exist a donor willing to finance this. Williams (2012) provides additional discussion of the practical considerations of innovation prizes.

These complications are one reason that AMCs and prizes do not play a larger role in innovation, though they were more prominent in the past. Using historical data from several countries where innovation prizes were used, Khan (2015) explains that the high transactions costs involved in administering these prizes limited their efficacy. Another concern, discussed in greater detail in Section 5, is the potential for free-riding on the incentives for innovation created by prizes by those who contribute nothing to its financing.

3.3. Functioning of capital markets

3.3.1. Markets for technology

Whether in the form of patents or prizes, pull policies require capital markets to function efficiently. That is, investors must be able to identify promising researchers and direct the necessary funds accordingly. In a large firm with existing products and cash flows, R&D can be financed internally. Small firms are usually more reliant on external sources of funding, like bank lending and venture capital. The cost of external capital has implications for entry and advantages to firm size (Froot et al., 1993).

The rate of entry of biotechnology start-ups since the mid-1970s suggests the availability of capital. However, this availability varies over time as well as across geographies. For example, Europe is perceived to have a financing gap relative to the US (Deu and da Silva, 2019).

Small firms can turn to another source of funding: licensing deals or partnerships with larger firms. Underlying the "market for technology" in pharmaceuticals is efficiency differences between small and large firms in different activities. Smaller firms may have an advantage in identifying novel drug candidates, but lack the complementary assets necessary to run large-scale clinical trials and commercialize them. Large, experienced firms may be better positioned to manage such trials, as well as navigate the complex regulatory approval process and pricing negotiations necessary to launch a new drug. In theory, the total cost of developing a drug is lower if the two firms specialize in these different activities, with the R&D specialist licensing out or selling the project to the marketing specialist at the stage at which the latter has an efficiency advantage.

It is important to note that, besides their direct role in providing innovation incentives, patents facilitate these relationships. Arrow's information paradox would otherwise hamper the disclosure of the necessary information to value a drug candidate. Thus, if one believes that the overall rate of innovation is higher with the vertical specialization just described, relative to a world in which innovation takes place inside vertically-integrated firms, patents have an indirect effect on innovation via this channel.

The optimal size and scope of pharmaceutical firms and the efficiency of markets for technology in pharmaceutical development remain open questions. Cockburn and Henderson (2001) provide evidence for limited scale and scope economies, but within a sample of large, vertically-integrated firms. Firm size partly explains differences in performance at different stages of clinical development (Grabowski and Kyle, 2012). Danzon et al. (2005) examine factors that determine gains from collaboration.

These and other results have implications for competition authorities if they consider how a merger or acquisition might affect innovation. Allain et al. (2015) suggest that, because of frictions in markets for technology, a reduction in the number of potential buyers of a drug development project may result in more efficient licensing of projects. More recently, Cunningham et al. (2021) highlight the risk that markets for technology could be detrimental to innovation if they take the form of "killer acquisitions," in which projects that could be future competitors to the acquiring firm are discontinued.

4. When are push policies effective?

Push policies to encourage innovation can be very general, such as R&D tax credits, or more targeted, such as grants or subsidies with specific aims. Relative to patents, government funding permits more control over the direction of research efforts, depending on how grants are structured. The nature of the research funded by governments often differs from that pursued by the private sector. Patents are supposed to protect inventions, not basic research. Because basic research generates more spillovers and firms have difficulty appropriating the benefits, the private sector generally invests more in applied research that is closer to the product market than does the public sector.[5] As Azoulay and Li (2020) explain, public research funding through grants is best suited to situations where appropriability is not possible (because the subject matter is not covered by patents) or not desirable (because cumulative research might be impeded, for example).

Push policies also interact with or complement many other policies. For example, immigration policies on visas available to foreign students or researchers are important (Ganguli et al., 2020), as is public support for institutions that increase access to knowledge (Furman and Stern, 2011). However, I focus in this section primarily on medical research funding in the form of grants, which is most relevant to pharmaceutical innovation.

4.1. Functioning of government payers

While the functioning of product markets is critical to the effectiveness of patents, it is obvious that push policies depend on political systems and bureaucracies that work well. A key difference between patents or prizes and push policies is that grants represent immediate budget outlays, and the government must be willing to pay for failure. Political pressures, whether to control government spending in general or to avoid wasteful spending on pet projects, introduce the risk that government support for a research program may be unstable. In addition, the administration of research grants requires certain competencies in evaluating and monitoring research.

[5] However, in recent years, private spending on basic research has exceeded US federal spending. In 2019, for example, federal funding was just under $22 billion, while firms in the US reported spending almost $26 billion (Wolfe, 2021).

Most of the empirical evidence on the effects of medical research funding concerns the US National Institutes of Health (NIH), which is responsible for about half of global public spending in this area (Moses et al., 2015). It is not clear to what extent the results of these studies can be generalized to other settings, with different political constraints and preferences. As noted earlier, many other US-specific factors may influence the allocation and outcomes associated with NIH grants.

These studies generally support the hypothesis that push policies result in more pharmaceutical innovation (Sampat, 2011). Indeed, the estimates of the rate of return to public funding are very high: Cockburn and Henderson (2000) describe their figure of 30% as an underestimate. Toole (2007) finds that the NIH funding that flows mainly to universities and non-profit institutions complements private-sector investment. Results using more recent data, and with new approaches to causal estimation, continue to show that NIH funding has large effects, with an additional $10 million yielding 2.3 more patents on average (Azoulay et al., 2019).

4.1.1. Information problems

Despite the encouraging evidence of the success of push funding, there may be some room for improvement. A government faces many of the same challenges in allocating grants as in funding an innovation prize. In particular, grants require the acquisition of more information: what innovation is desired; the level of funding necessary to achieve it; and the most qualified researchers for that funding.

In general, NIH funding appears to respond to domestic need, as least as measured by burden of disease (Lichtenberg, 2001). Because the NIH depends on the elected US Congress to allocate its budget, it is not surprising that there is a relationship between the needs of American voters and the direction of research funding. However, this suggests that research efforts financed by push incentives are likely to be tilted towards the needs of relatively rich, developed countries – that is, it is subject to a common criticism of the patent system. Even within the US population, Lichtenberg (2001) finds that public research funding does not respond in the same way to the disease burden of non-whites. Because much NIH funding is bottom-up, it is not clear to what extent these funding patterns reflect the demand for research in specific areas or the supply of researchers working in those areas.[6]

More than 58,000 research project grant applications were submitted to the NIH in 2021,[7] and identifying the most deserving is no small task. The NIH has expert committees and peer reviewers to undertake this. Azoulay and Li (2020) suggest that scale in this review may be one reason that most European countries did not employ such a system prior to the establishment of the European Research Council. NIH reviewers appear to be good at this task (Li and Agha, 2015), even if they show some bias towards their research domains (Li, 2017). There is, however, some concern that this system of grant allocation favors older, established scientists, with long-run consequences for innovative output (Jones, 2011; Levitt and Levitt, 2017). In addition, governments often impose some limits on who may apply for funding. Even for large countries with a deep pool of qualified applicants, expertise may be outside their borders.

Historically the NIH has enjoyed remarkable bipartisan support, and the use of peer review to choose the recipients of its grants should limit political influence. However, Hegde and Mowery (2008) and Hegde (2009) show that funding tends to flow to "relatively weak" institutions located in the districts of powerful legislators. Lobbying by private interest groups associated with specific diseases also occurs. Although Hegde and Sampat (2015) do not find large distortions associated with these efforts (in part because lobbying increases with the burden of a disease), it does result in more "earmarked" funding by Congress.

4.2. Functioning of technology transfer

Basic research is expected to generate knowledge spillovers. Increasingly, rather that leaving those spillovers to chance, some government policy has the aim of ensuring that public research funding generates quantifiable benefits to the private sector. In the case of biomedical research and pharmaceuticals, the links between public funding and commercialized products are relatively easy to measure. Stevens et al. (2011), among others, document that public sector research institutions are the origin of a substantial fraction of new drugs brought to market. While economists often worry about crowding out of private sector activity by public spending, the collaboration between the two and the documented spillovers suggests this is not a significant problem in pharmaceutical research.[8]

Ensuring that technology transfer occurs requires the alignment of multiple stakeholder incentives. This article makes no attempt to provide a full treatment of this issue, except to note the (often controversial) role of intellectual property rights. The Bayh–Dole Act of 1984 permitted US universities to retain the patent rights on inventions funded by federal money. This spawned the establishment of university technology transfer offices tasked with finding licensees for those patents, and generated many spin-offs dedicated to commercializing the research of faculty members.

One concern is that combining push funding with the pull incentive provided by patents has patients or taxpayers paying twice for pharmaceuticals whose development can be traced to public funding: first by paying taxes to support government-funded research, and second by paying high prices on the patented therapies that result. One notable example is the case

[6] The NIH also has top-down funding; see Sampat (2012).

[7] FY 2021 By the Numbers: Extramural Grant Investments in Research.

[8] Goolsbee (1998) suggests one mechanism for crowding out that could apply, however. He finds that increased government spending on R&D drives up the wages of scientists and engineers, increasing costs for the private sector as well as the public.

of a Zika vaccine initially developed by the researchers in the US Army with financing from the Biomedical Advanced Research and Development Authority (BARDA). Because the US military is not usually in the business of drug development and manufacturing, it sought a licensee to perform the necessary clinical trials and commercialize the vaccine. Sanofi, a large French pharmaceutical firm, agreed to an exclusive license in July 2016. However, Senator Bernie Sanders (D-Vermont) and other lawmakers criticized this arrangement several months later; Sanders has proposed a number of bills over the years to limit the prices a licensee may charge in the US for a drug that benefited from public funding. Sanofi dropped its efforts to develop the vaccine soon after, and as of the end of 2021, no Zika vaccine has reached the market.[9]

A second worry is that while patents might facilitate technology transfer between universities and the private sector, the alternative – putting the results of research in the public domain, accessible to all – could result in broader use. While many key technologies in biotechnology have been licensed out on a non-exclusive basis, in other cases, no licensee may be willing to license pharmaceutical patents without exclusivity. This exclusivity, of course, brings with it all the potential problems associated with patents. Perhaps recognizing the importance of private sector involvement in commercializing many pharmaceutical innovations, the NIH has been reluctant to exercise its march-in rights[10] to interfere in the licensing of pharmaceutical patents (Treasure et al., 2015).

Finally, Bayh–Dole and university patenting raise important questions about the appropriate balance of basic and applied research more broadly. Universities with many patents are likely to have a more commercial orientation, because basic science is harder to protect with patents. While Thursby and Thursby (2011) argue that the Bayh–Dole Act did not compromise basic research at universities, ? suggest that universities now use patents as part of their pursuit of revenue rather than to encourage the use of federally-funded research.

5. “Multilateral” innovation policies

5.1. Spillovers and free-riding

Much of the discussion above focused on domestic or unilateral innovation policies to encourage the development of new pharmaceuticals. Even if needs differ across countries, and the therapeutic efficacy may also vary across populations for reasons related to genetics or the interaction with other location-specific factors, most drugs are global products. Transportation and adoption costs are relatively low. Thus, the fruits of innovation policies can be consumed beyond the borders of the country that pushed or pulled them.

Few countries have the market size or budget to unilaterally shift innovation incentives through a policy change. For example, one additional year of patent protection in Canada would change very little a firm’s expected profits from investing in a drug development project; Canadian patients or government payers, however, would likely see higher prices during that additional year. Similarly, a doubling of medical research funding in most countries might have the effect of attracting more scientists and changing the location of research, but is unlikely to change the global level enough to have a measurable impact on innovation. One reason that so much empirical study focuses on the US is that its size provides some hope of measuring the effect of innovation policy.

This is not to suggest that countries have no incentive to implement costly innovation policies; historically, patent protection has been introduced in countries for a variety of strategic motivations (Moser, 2013). Strong intellectual property rights yield benefits to a country in the form of increased foreign direct investment (Branstetter et al., 2006) and trade in knowledge-intensive products (Delgado et al., 2013). Qian (2007) finds that pharmaceutical patent protection stimulates domestic R&D in relatively developed countries, but the benefits are much lower for developing countries (Gamba, 2017). Countries also benefit from local knowledge spillovers generated by academic research, and so have an interest in public funding (Hausman, 2021).

Nevertheless, spillovers and the limited effects of most unilateral policy changes create a situation in which the potential for free-riding exists. Kyle et al. (2017) provide some evidence that governments adjust their funding for disease-specific research in response to changes in US spending. Pertile et al. (2018) show that countries also free-ride on the incentives created by drug prices in a study of 25 OECD countries – something many US political figures and administrations have complained about. Free-riding may also be an explanation for the limited number of innovation prizes for pharmaceuticals.

5.2. Coordination and commitment

There are obvious similarities between the problems just described and those associated with policies to address climate change. Many countries are too small for unilateral adjustments to their greenhouse gas emissions to matter, and any benefits are enjoyed by countries that have not paid the costs to achieve them. Mechanisms to coordinate international efforts, and to commit to these efforts, are important both for climate change and for innovation.

Multilateral and bilateral trade agreements negotiated over the last several decades – and even further back – often include intellectual property provisions. These can be controversial. The Trade Related Agreement on Intellectual Property

[9] Sanofi pulls out of Zika vaccine collaboration as feds gut its R&D contract.

[10] Bayh–Dole allows the funding agency to grant additional licenses under certain conditions, including if the university fails to satisfy the health and safety needs of consumers through its management of the patent.

Rights (TRIPS), with which members of the World Trade Organization must comply, requires national patent laws to include protection for pharmaceutical products, raising fears that patents would limit access to essential treatments. While the optimal length and breadth of patent protection almost certainly changes with a country's level of development, one argument for imposing a global minimum is that this limits the ability of some countries to free-ride on the incentives for innovation created by patents in other countries.

The European Union provides an example of a coordination mechanism for both pull and push policies. Member states now provide a uniform term of market exclusivity for new drugs (8 years for data protection, plus two additional years of market exclusivity). Europe also coordinates public funding for research through the European Research Council (ERC). Other international organizations, such as the OECD and WHO, can contribute to policy coordination as well.

As with climate change, however, credible commitments are difficult. As part of the Lisbon Strategy of 2000, European countries promised to increase R&D investment to 3% of GDP by 2010. By 2019, the EU average was 2.19%, with only three countries above the 3% goal.

5.3. Relevance to COVID

Two years into the COVID-19 pandemic, what are the lessons for innovation policy? The good news is that several vaccines were developed, and in record time. In December 2021, regulators in the US, Europe, South Korea, and Israel approved a new treatment for those infected. Public funding, both pre-pandemic and in response, contributed to the basic science behind some of these technologies (Lalani et al., 2021; Cross et al., 2021). Government commitments to purchase large quantities no doubt pulled investment as well.

The bad news is that access to both vaccines and treatments is not universal. India and South Africa, joined by many other countries (including even the US), have proposed a temporary waiver of intellectual property rights on coronavirus vaccines. Others argue that supply constraints in production are the bottleneck, and others that a patent waiver alone would not enable developing countries to produce these vaccines because of the complexities of technology transfer. A lack of international coordination has also contributed to supply problems.

The COVID experience makes even more stark some of the tensions and challenges in innovation policy for pharmaceuticals. For example, in choosing recipients of public funding, governments may be uninformed and choose unwisely, as happened in the case of Emergent Biosolutions. We don't yet know whether Operation Warp Speed and other efforts funded the best researchers, or the most politically connected. The collaboration between the NIH and Moderna that contributed to the latter's mRNA vaccine is now the subject of a patent dispute. Given the massive market for COVID vaccines and advance purchase commitments, patent protection may have played a minor role in pulling innovation – but the fear of compulsory licensing or a patent waiver may well depress incentives to develop treatments that are easier to manufacture. The private sector has invested little in exploring the use of older, off-patent drugs to treat COVID.

The COVID crisis will certainly be used by economists and other to study the effects of many different policies. Already, there are proposals for improving the production and distribution of vaccines before the next pandemic (Ahuja et al., 2021). Perhaps we will see innovation in innovation policy for pharmaceuticals too.

6. Conclusion

I argue that innovation policies are working well overall in the pharmaceutical sector. Where they are not, particularly in the case of patents, it may be more important to focus on fixing problems in product markets before making radical changes to patent policy: patents should be more effective at pulling in valuable innovation when downstream markets are efficient, rewarding the best treatments with the highest profits. In some contexts, an innovation prize may be preferable. The difficulties in designing such a prize, and in attracting funding commitments from multiple countries, remain a significant challenge.

Many studies have shown large returns on investments in public sector research, especially in biomedical fields. The political appetite for push policies like this may be greater than for expanding pull policies like patents. The COVID pandemic has motivated many countries to announce an increase support for medical research. While a shared global commitment to funding vital research is heartening, spending should be considered a means to an end, not the objective itself. Efficient allocation also requires careful attention to the details of policy design.

Despite a great deal of empirical work evaluating the effects of innovation policy, we have little evidence on the policies for which marginal costs equal marginal benefits. We also know too little about how innovation policies interact with others, and how this might explain both the choice of policies and their effects in different countries. With increased globalization, the strategic interactions between countries are worth additional study as well.

CRediT authorship contribution statement

Margaret K. Kyle: Conceptualization, Writing – original draft.

References

Acemoglu, D., Linn, J., 2004. Market size in innovation: theory and evidence from the pharmaceutical industry. Q. J. Econ. 119 (3), 1049–1090.

Ahuja, A., Athey, S., Baker, A., Budish, E., Castillo, J.C., Glennerster, R., Kominers, S.D., Kremer, M., Lee, J., Prendergast, C., Snyder, C.M., Tabarrok, A., Tan, B.J., Wiecek, W., 2021. Preparing for a pandemic: accelerating vaccine availability. AEA Pap. Proc. 111, 331–335. doi:10.1257/pandp.20211103.
Allain, M.-L., Henry, E., Kyle, M., 2015. Competition and the efficiency of markets for technology. Manag. Sci. 62 (4), 1000.
Azoulay, P., 2002. Do pharmaceutical sales respond to scientific evidence? J. Econ. Manag. Strategy 11 (4), 551–594.
Azoulay, P., Li, D., 2020. Scientific Grant Funding. Working Paper 26889. National Bureau of Economic Research doi:10.3386/w26889.
Azoulay, P., Zivin, J.G., Li, D., Sampat, B., 2019. Public R&D investments and private sector patenting: Evidence from NIH funding rules. Rev. Econ. Stud. 86 (1), 117–152.
Baicker, K., Goldman, D., 2011. Patient cost-sharing and healthcare spending growth. J. Econ. Perspect. 25 (2), 47–68. http://www.jstor.org/stable/23049453
Balfour-Lynn, I.M., King, J.A., 2020. CFTR modulator therapies - effect on life expectancy in people with cystic fibrosis. Paediatr Respir Rev doi:10.1016/j.prrv.2020.05.002.
Bennato, A.R., Valletti, T., 2014. Pharmaceutical innovation and parallel trade. Int. J. Ind. Organ. 33, 83–92. doi:10.1016/j.ijindorg.2014.02.009.
Bennett, D., Hung, C.-L., Lauderdale, T.-L., 2015. Health care competition and antibiotic use in taiwan. J. Ind. Econ. 63 (2), 371–393. http://www.jstor.org/stable/44077361
Blume-Kohout, M.E., Sood, N., 2013. The impact of medicare part D on pharmaceutical R&D. J. Public Econ. 97, 327–336.
Boldrin, M., Levine, D.K., 2013. The case against patents. J. Econ. Perspect. 27 (1), 3–22. doi:10.1257/jep.27.1.3.
Branstetter, L.G., Fisman, R., Foley, C.F., 2006. Do stronger intellectual property rights increase international technology transfer? Empirical evidence from U. S. Firm-level panel data*. Q. J. Econ. 121 (1), 321–349. doi:10.1093/qje/121.1.321.
Branstetter, Lee G, Chatterjee, Chirantan, Higgins, Matthew, 2016. Regulation and Welfare: Evidence from Paragraph IV Generic Entry in the Pharmaceutical Industry. RAND Journal of Economics 47 (4), 857–890.
Budish, E., Roin, B.N., Williams, H., 2015. Do fixed patent terms distort innovation? Evidence from cancer clinical trials. Am. Econ. Rev. 105 (7), 2044–2085.
Carrera, M., Goldman, D.P., Joyce, G., Sood, N., 2018. Do physicians respond to the costs and cost-sensitivity of their patients? Am. Econ. J. 10 (1), 113–152. https://www.jstor.org/stable/26529010
Ching, A.T., Ishihara, M., 2012. Measuring the informative and persuasive roles of detailing on prescribing decisions. Manag. Sci. 58 (7), 1374–1387.
Cockburn, I.M., Henderson, R.M., 2000. Publicly funded science and the productivity of the pharmaceutical industry. Innov. Policy Econ. 1, 1–34. http://www.jstor.org/stable/25056140.
Cockburn, I.M., Henderson, R.M., 2001. Scale and scope in drug development: unpacking the advantages of size in pharmaceutical research. J. Health Econ. 20 (6), 1033–1057. doi:10.1016/S0167-6296(01)00108-4.
Cohen, J., Dupas, P., Schaner, S., 2015. Price subsidies, diagnostic tests, and targeting of malaria treatment: evidence from a randomized controlled trial. Am. Econ. Rev. 105 (2), 609–645. http://www.jstor.org/stable/43495394
Cross, S., Rho, Y., Reddy, H., Pepperrell, T., Rodgers, F., Osborne, R., Eni-Olotu, A., Banerjee, R., Wimmer, S., Keestra, S., 2021. Who funded the research behind the Oxford-AstraZeneca COVID-19 vaccine? BMJ Global Health 6 (12). doi:10.1136/bmjgh-2021-007321.
Cunningham, C., Ederer, F., Ma, S., 2021. Killer acquisitions. J. Polit. Econ. 129 (3), 649–702. doi:10.1086/712506.
Cutler, D., Skinner, J.S., Stern, A.D., Wennberg, D., 2019. Physician beliefs and patient preferences: a new look at regional variation in health care spending. Am. Econ. J. 11 (1), 192–221. doi:10.1257/pol.20150421.
Danzon, P.M., Nicholson, S., Pereira, N.S., 2005. Productivity in pharmaceutical-biotechnology R&D: the role of experience and alliances. J. Health Econ. 24 (2), 317–339. doi:10.1016/j.jhealeco.2004.09.006.
Danzon, P.M., Pauly, M.V., 2002. Health insurance and the growth in pharmaceutical expenditures. J. Law Econ. 45 (S2), 587–613. http://www.jstor.org/stable/10.1086/368005
Darrow, J.J., Kesselheim, A.S., 2020. Incentivizing antibiotic development: why isn't the generating antibiotic incentives now (GAIN) act working? Open Forum Infect. Dis. 7 (1). doi:10.1093/ofid/ofaa001. Ofaa001
Datta, A., Dave, D., 2017. Effects of physician-directed pharmaceutical promotion on prescription behaviors: longitudinal evidence. Health Econ. 26 (4), 450–468.
Delgado, M., Kyle, M., McGahan, A., 2013. Intellectual property protection and the geography of trade. J. Ind. Econ. 61 (3), 733–762.
Deu, F.L., da Silva, J.S., 2019. Biotech in Europe: A Strong Foundation for Growth and Innovation. Technical Report. McKinsey & Company. https://www.mckinsey.com/industries/life-sciences/our-insights/biotech-in-europe-a-strong-foundation-for-growth-and-innovation
DiMasi, J.A., Grabowski, H.G., Hansen, R.W., 2016. Innovation in the pharmaceutical industry: new estimates of R&D costs. J. Health Econ. 47, 20–33. doi:10.1016/j.jhealeco.2016.01.012.
Dranove, D., 1998. Is there underinvestment in R&D about prevention? J. Health Econ. 17 (1), 117–127. doi:10.1016/S0167-6296(97)00015-5.
Drummond, M., Towse, A., 2012. Is it time to reconsider the role of patient co-payments for pharmaceuticals in Europe? Eur. J. Health Econ. 13 (1), 1–5. http://www.jstor.org/stable/41408294
Dubois, P., Sæthre, M., 2020. On the effect of parallel trade on manufacturers' and retailers' profits in the pharmaceutical sector. Econometrica 88 (6), 2503–2545.
Eisenberg, R.S., 2012. Patents and regulatory exclusivity. In: Danzon, P.M., Nicholson, S. (Eds.), The Oxford Handbook of the Economics of the Biopharmaceutical Industry. Oxford University Press, Oxford, pp. 167–198.
Epstein, A.J., Ketcham, J.D., 2014. Information technology and agency in physicians' prescribing decisions. RAND J. Econ. 45 (2), 422–448.
Falcaro, M.e.a., 2021. The effects of the national HPV vaccination programme in england, uk, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. Lancet 398 (10316), 2084–2092.
Finkelstein, A., 2004. Static and dynamic effects of health policy: evidence from the vaccine industry. Q. J. Econ. (May) 527–564.
Froot, K.A., Scharfstein, D.S., Stein, J.C., 1993. Risk management: coordinating corporate investment and financing policies. J. Finance 48 (5), 1629–1658. http://www.jstor.org/stable/2329062
Furman, J.L., Stern, S., 2011. Climbing atop the shoulders of giants: the impact of institutions on cumulative research. Am. Econ. Rev. 101 (5), 1933–1963. doi:10.1257/aer.101.5.1933.
Gaessler, F., Wagner, S., 2020. Patents, data exclusivity, and the development of new drugs. Rev. Econ. Stat. 1–49. doi:10.1162/rest_a_00987.
Galasso, A., Schankerman, M., 2014. Patents and cumulative innovation: causal evidence from the courts. Q. J. Econ. 130 (1), 317–369. doi:10.1093/qje/qju029.
Gamba, S., 2017. The effect of intellectual property rights on domestic innovation in the pharmaceutical sector. World Dev. 99 (C), 15–27. https://EconPapers.repec.org/RePEc:eee:wdevel:v:99:y:2017:i:c:p:15-27
, 2020. In: Ganguli, I., Kahn, S., MacGarvie, M. (Eds.), The Roles of Immigrants and Foreign Students in US Science, Innovation, and Entrepreneurship. University of Chicago Press.
Garthwaite, C., Sachs, R., Stern, A.D., 2021. Which Markets (Don't) Drive Pharmaceutical Innovation? Evidence From U.S. Medicaid Expansions. Working Paper 28755. National Bureau of Economic Research doi:10.3386/w28755.
Geoffard, P.-Y., Philipson, T., 1997. Disease eradication: private versus public vaccination. Am. Econ. Rev. 87 (1), 222–230.
Gilchrist, D.S., 2016. Patents as a spur to subsequent innovation? Evidence from pharmaceuticals. Am. Econ. J. 8 (4), 189–221. doi:10.1257/app.20150373.
Goolsbee, A., 1998. Does R&D policy primarily benefit scientists and engineers? Am. Econ. Rev. 88 (2), 298–302.
Grabowski, H.G., Kyle, M.K., 2012. Mergers, acquisitions and alliances. In: Danzon, P.M., Nicholson, S. (Eds.), The Oxford Handbook of the Economics of the Biopharmaceutical Industry. Oxford University Press, Oxford, pp. 552–577.
Guedj, I., Scharfstein, D., 2004. Organizational Scope and Investment: Evidence from the Drug Development Strategies and Performance of Biopharmaceutical Firms. Working Paper 10933. National Bureau of Economic Research.
Gupta, C., 2020. One product, many patents: Imperfect intellectual property rights in the pharmaceutical industry. https://doi.org/10.2139/ssrn.3748158.
Hausman, N., 2021. University innovation and local economic growth. Rev. Econ. Stat. 1–46. doi:10.1162/rest_a_01027.

Hawkins, S.S., Horvath, K., Cohen, J., Pace, L.E., Baum, C.F., 2021. Associations between insurance-related affordable care act policy changes with HPV vaccine completion. BMC Public Health 21 (1), 304. doi:10.1186/s12889-021-10328-4.
Hegde, D., 2009. Political influence behind the veil of peer review: an analysis of public biomedical research funding in the united states. J. Law Econ. 52 (4), 665–690.
Hegde, D., Mowery, D.C., 2008. Politics and funding in the U.S. public biomedical R&D system. Science 322 (5909), 1797–1798.
Hegde, D., Sampat, B., 2015. Can private money buy public science? Disease group lobbying and federal funding for biomedical research. Manag. Sci. 61 (10), 2281–2298.
Hemphill, C.S., Sampat, B.N., 2012. Evergreening, patent challenges, and effective market life in pharmaceuticals. J. Health Econ. 31 (2), 327–339.
Iizuka, T., 2007. Experts' agency problems: evidence from the prescription drug market in Japan. RAND J. Econ. 38 (3), 844–862.
Jacobson, M., Earle, C.C., Price, M., Newhouse, J.P., 2010. How Medicare's payment cuts for cancer chemotherapy drugs changed patterns of treatment. Health Aff. 29 (7), 1391–1399. doi:10.1377/hlthaff.2009.0563.
Jena, A., Philipson, T., 2009. Endogenous Cost-Effectiveness Analysis in Health Care Technology Adoption. National Bureau of Economic Research Working Paper 15032.
Jones, B.F., 2011. As science evolves, how can science policy? Innov. Policy Econ. 11 (1), 103–131. http://www.jstor.org/stable/10.1086/655820
Khan, B.Z., 2015. Inventing prizes: a historical perspective on innovation awards and technology policy. Bus. Hist. Rev. 89 (4), 631–660. doi:10.1017/S0007680515001014.
Kiriyama, N., 2012. Trade and Innovation: Synthesis Report. OECD Trade Policy Papers.
Kremer, M., Glennerster, R., 2004. Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases. Princeton University Press, Princeton.
Kremer, M., Levin, J., Snyder, C.M., 2020. Advance market commitments: insights from theory and experience. AEA Pap. Proc. 110, 269–273. doi:10.1257/pandp.20201017.
Kremer, M., Snyder, C., 2015. Preventives versus treatments. Q. J. Econ. 130 (3), 1167–1239. https://EconPapers.repec.org/RePEc:oup:qjecon:v:130:y:2015:i:3:p:1167-1239.
Kremer, M.R., 1998. Patent buyouts: a mechanism for encouraging innovation. Q. J. Econ. 113 (4), 1137–1167.
Kyle, M., 2007. Pharmaceutical price controls and entry strategies. Rev. Econ. Stat. 89 (1), 88–99.
Kyle, M., 2018. Are important innovations rewarded? Evidence from pharmaceutical markets. Rev. Ind. Organ. 53 (1), 211–234.
Kyle, M., Ridley, D., Zhang, S., 2017. Strategic interaction among governments in the provision of a global public good. J. Public Econ. 156, 185–199.
Kyle, M., Williams, H., 2017. Is American health care uniquely inefficient? Evidence from prescription drugs. Am. Econ. Rev. 107 (5), 486–490. doi:10.1257/aer.p20171086.
Kyle, M.K., 2011. Strategic responses to parallel trade. B.E. J. Econ. Anal. Policy 11 (2).
Kyle, M.K., Allsbrook, J.S., Schulman, K.A., 2008. Does reimportation reduce price differences for prescription drugs? Lessons from the European Union. Health Serv. Res. 43 (4), 1308–1324. doi:10.1111/j.1475-6773.2008.00838.x.
Kyle, M.K., McGahan, A.M., 2012. Investments in pharmaceuticals before and after TRIPS. Rev. Econ. Stat. 94 (4), 1157–1172.
Lalani, H.S., Avorn, J., Kesselheim, A.S., 2021. US taxpayers heavily funded the discovery of COVID-19 vaccines. Clin. Pharmacol. Ther. doi:10.1002/cpt.2344.
Levin, R.C., Klevorick, A.K., Nelson, R.R., Winter, S.G., 1987. Appropriating the returns from industrial research and development. Brook. Pap. Econ. Act. 3, 783–820.
Levitt, M., Levitt, J.M., 2017. Future of fundamental discovery in US biomedical research. Proc. Natl. Acad. Sci. 114 (25), 6498–6503. doi:10.1073/pnas.1609996114.
Li, D., 2017. Expertise versus bias in evaluation: evidence from the NIH. Am. Econ. J. 9 (2), 60–92.
Li, D., Agha, L., 2015. Big names or big ideas: do peer review panels select the best science proposals? Science 348 (6233), 434–438.
Li, X., Lo, A.W., Thakor, R.T., 2021. Paying off the Competition: Market Power and Innovation Incentives. National Bureau of Economic Research.
Lichtenberg, F.R., 2001. the allocation of publicly funded biomedical research. In: Cutler, D.M., Berndt, E.R. (Eds.), Medical Care Output and Productivity.
Love, J., 2011. De-linking R&D Costs from Product Prices. http://www.who.int/phi/news/phi_cewg_1stmeet_10_KEI_submission_en.pdf.
Macfarlane, J., Holmes, W., Macfarlane, R., Britten, N., 1997. Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. BMJ 315 (7117), 1211–1214. doi:10.1136/bmj.315.7117.1211.
Manning, W.G., Newhouse, J.P., Duan, N., Keeler, E.B., Leibowitz, A., 1987. Health insurance and the demand for medical care: evidence from a randomized experiment. Am. Econ. Rev. 77 (3), 251–277.
Mazzucato, M., Li, H.L., Darzi, A., 2020. Is it time to nationalise the pharmaceutical industry? BMJ 368. doi:10.1136/bmj.m769.
Moser, P., 2013. Patents and innovation: evidence from economic history. J. Econ. Perspect. 27 (1), 23–44. doi:10.1257/jep.27.1.23.
Moses Hamilton, I., Matheson, D.H.M., Cairns-Smith, S., George, B.P., Palisch, C., Dorsey, E.R., 2015. The anatomy of medical research: US and international comparisons. JAMA 313 (2), 174–189. doi:10.1001/jama.2014.15939.
de Mouzon, O., Dubois, P., Morton, F.S., Seabright, P., 2015. Market size and pharmaceutical innovation. RAND J. Econ. 46 (4), 844–871.
Nicod, E., 2017. Why do health technology assessment coverage recommendations for the same drugs differ across settings? Applying a mixed methods framework to systematically compare orphan drug decisions in four european countries. Eur. J. Health Econ. 18 (6), 715–730. http://www.jstor.org/stable/44320136
Panattoni, L.E., 2011. The effect of Paragraph IV decisions and generic entry before patent expiration on brand pharmaceutical firms. J. Health Econ. 30 (1), 126–145. doi:10.1016/j.jhealeco.2010.09.004.
Pertile, P., Gamba, S., Forster, M., 2018. Free-Riding in Pharmaceutical Price Regulation: Theory and Evidence. Discussion Papers. Department of Economics, University of York. https://EconPapers.repec.org/RePEc:yor:yorken:18/04
Prasad, V., Vandross, A., Toomey, C., Cheung, M., Rho, J., Quinn, S., Chacko, S.J., Borkar, D., Gall, V., Selvaraj, S., Ho, N., Cifu, A., 2013. A decade of reversal: an analysis of 146 contradicted medical practices. Mayo Clin. Proc. 88 (8), 790–798. doi:10.1016/j.mayocp.2013.05.012.
Qian, Y., 2007. Do additional national patent laws stimulate domestic innovation in an international patenting environment? Rev. Econ. Stat. 89 (3), 436–453.
Reisinger, M., Saurí, L., Zenger, H., 2019. Parallel imports, price controls, and innovation. J. Health Econ. 66, 163–179. doi:10.1016/j.jhealeco.2019.05.002.
Ridley, D.B., Grabowski, H.G., Moe, J.L., 2006. Developing drugs for developing countries. Health Aff. 25 (2), 313–324.
Sampat, B., 2011. Measuring the Impacts of Federal Investments in Research: A Workshop Summary. The National Academies Press, pp. 153–192.
Sampat, B., Williams, H.L., 2019. How do patents affect follow-on innovation? Evidence from the human genome. Am. Econ. Rev. 109 (1), 203–236. doi:10.1257/aer.20151398.
Sampat, B.N., 2012. Mission-oriented biomedical research at the NIH. Res. Policy 41 (10), 1729–1741. doi:10.1016/j.respol.2012.05.013. The need for a new generation of policy instruments to respond to the Grand Challenges
Sarpatwari, A., Beall, R.F., Abdurrob, A., He, M., Kesselheim, A.S., 2018. Evaluating the impact of the orphan drug act's seven-year market exclusivity period. Health Aff. 37 (5), 732–737. doi:10.1377/hlthaff.2017.1179. PMID: 29733729
Sorensen, A.T., 2000. Equilibrium price dispersion in retail markets for prescription drugs. J. Polit. Econ. 108 (4), 833–850. http://www.jstor.org/stable/10.1086/316103
Stevens, A.J., Jensen, J.J., Wyller, K., Kilgore, P.C., Chatterjee, S., Rohrbaugh, M.L., 2011. The role of public-sector research in the discovery of drugs and vaccines. N. Engl. J. Med. 364 (6), 535–541. doi:10.1056/NEJMsa1008268. PMID: 21306239
Thursby, J.G., Thursby, M.C., 2011. Has the Bayh–Dole act compromised basic research? Res. Policy 40 (8), 1077–1083. doi:10.1016/j.respol.2011.05.009. Special Issue: 30 Years After Bayh–Dole: Reassessing Academic Entrepreneurship
Toole, A.A., 2007. Does public scientific research complement private investment in research and development in the pharmaceutical industry? J. Law Econ. 50 (1), 81–104. doi:10.1086/508314.

Treasure, C.L., Avorn, J., Kesselheim, A.S., 2015. Do march-in rights ensure access to medical products arising from federally funded research? a qualitative study. Milbank Q 93 (4), 761–787. doi:10.1111/1468-0009.12164.
Williams, H., 2012. Innovation inducement prizes: connecting research to policy. J. Policy Anal. Manag. 31 (3), 752–776. http://www.jstor.org/stable/41653827.
Williams, H.L., 2013. Intellectual property rights and innovation: evidence from the human genome. J. Polit. Econ. 121 (1), 1–27. doi:10.1086/669706.
Wolfe, R. M., 2021. Infobrief NSF 22–303. http://ncses.nsf.gov/pubs/nsf22303.
World Health Organization, 2016. Global Health Sector Strategy on Viral Hepatitis 2016–2021. Towards Ending Viral Hepatitis. Technical documents.
Xue, Q.C., Ouellette, L.L., 2020. Innovation policy and the market for vaccines. J. Law Biosci. 7 (1). doi:10.1093/jlb/lsaa026.
Yin, W., 2008. Market incentives and pharmaceutical innovation. J. Health Econ. 27 (4), 1060–1077.