White Paper: Pharmaceutical Regulation and Off-Label Uses

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Abstract

This White Paper reviews the empirical evidence on pharmaceutical regulation and private research investments from the health economics and health policy literature regarding off-label drug use and related topics. First, off-label use is defined and the rationale for government regulation is reviewed. The subsequent sections brings evidence from the literature to bear on pharmaceutical regulation, promotion, and private investments. Finally, the concluding section lists useful datasets for researchers interested in studying off-label use.

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1 Introduction

In the United States, the Food and Drug Administration (FDA) regulates the entry and marketing of new medical products to ensure that they are safe and effective. This regulatory regime may have substantial implications for firms' investment decisions, particularly in the case of uses of drugs for indications not approved by the FDA, or "off-label" drug use.[1] The current regulatory regime creates incentives and disincentives for manufacturers to seek FDA approval for new uses of approved products (Friedman, 1996). Incentives include increased sales due to the ability to legally market the drug for the new use and the increased likelihood of reimbursement by third-party insurance payers. Disincentives include high costs of FDA re-approval and the fact that physicians can legally prescribe a drug for non-FDA approved uses.

Profit-maximizing firms must weigh the expected benefits of seeking approval for additional indications against the expected gains of bypassing the re-approval process and expanding their off-label markets under marketing constraints. Such off-label promotion can take the form of conducting exploratory studies not intended to support a subsequent FDA approval (Eisenberg, 2005). In describing the trade-off, Malani and Philipson (2012) state, "A company will consider the use for which providing safety and efficacy is easiest as well as the use for which marketing is the most important."

This has important consequences for regulators, health care payers, and consumers, each of which have a unique set of goals: regulators demand rigorous evidence of safety and efficacy, payers want to pay for products with proven quality, and consumers (physicians, patients) want access to appropriate treatments and relevant information (Stafford, 2008). Central to this debate is the role of information for clinical decision-making, and the role and relevance of regulation in shaping what information to gather and under what conditions to make that information available to the public.

This White Paper reviews the empirical evidence on pharmaceutical regulation and private investments from the health economics and health policy literature regarding off-label use and related topics. In the next section, off-label use is defined and the rationale for government regulation is reviewed. The following sections brings evidence from the literature to bear on pharmaceutical regulation, promotion, and private investments. Finally, the concluding section lists useful datasets for researchers interested in studying off-label use.

[1] Unless otherwise noted, "drugs" refers to drugs, biologics, and medical devices.

2 Off-Label Uses

The practice of using health care technologies for unapproved uses is common, with estimates ranging from 20% to 39% (Bradford et al., 2014; Conti et al., 2013; Molitor and Agha, 2012; Radley et al., 2006). Such use is particularly common among therapies for cancer, cardiovascular diseases, and psychiatric diseases. There are several reasons for off-label use (Wittich et al., 2012). First, FDA-approved therapies might not exist for the treated population's specific disease. Second, physicians might substitute within a class of medication if one medication is approved for a particular use and others are not. Third, the features of two conditions might be similar and physicians may use one approved drug for both conditions. For example, off-label psychiatric drug use is common in children because mental illnesses are difficult to diagnose and children are rarely included in clinical trials for drug approval (Lee et al., 2012). Many mental illnesses share the same symptoms and are biochemically related, motivating physicians to use one drug approved for a particular condition in patients with a related illness.[2]

3 Rationale for Government Regulation

Given the influence of the existing regulatory environment in shaping investment incentives, it is important to understand the efficiency rationale for government regulation of information about the safety and efficacy of new health care technologies. The rationale results from the fact that pharmaceutical markets may exhibit a type of market failure known as "asymmetric information." New medical technologies are "experience goods" or "credence goods" – their risks and benefits cannot be ascertained through examination and sometimes, even after consumption (Nelson, 1970). Under asymmetric information, an "Akerlof-style" lemons market can result: here, a tension arises between buyers who would like more quality information about products and low quality sellers would like to pool with high-quality sellers (Akerlof, 1970). Without a credible guarantee of product quality, the market may unravel: buyers, realizing that low-quality sellers are pooling with high quality sellers, are only willing to pay the average quality of the goods. As a result, sellers with higher than average quality products leave the market. In Akerlof's model of used cars, this process repeats until there are no more transactions in the market. In practice, the markets for medicines do not necessarily shrink, but the market for quality products may (Katz, 2007).[3]

[2]The prevalence of off-label use depends on a physician's propensity to prescribe a drug with limited evidence of safety and efficacy. In practice, physicians who engage in off-label use are rarely accused of medical malpractice. The process of informed consent does not require physicians to disclose that a drug is being used off-label. Further, off-label use is not necessarily negligent if the off-label use is included in the current standard of practice.

[3]The market for quality dietary supplements provides a potentially interesting case study. The Dietary Supplement Health and Education Act of 1994 (DSHEA) created a new regulatory structure for dietary supplements, apart from drugs. Under DSHEA, manufacturers of dietary supplement containing ingredients already on the market no longer have to demonstrate safety and efficacy through clinical trials before marketing their products. Geller et al. (2015) note that the number of dietary supplement products rose from 4000 to 55,000 between 1994 and 2012, while an estimated

One solution to this market failure is the provision of information. Given the public good nature of information, the government can require firms to produce information as a condition of market entry and regulating how the information is disseminated. This can result in efficiency gains through improved sorting between patients and drugs, encouraging manufacturers to improve quality, and forcing low-quality manufacturers to exit the market (Dranove and Jin, 2010).

In addition to faciliation of consumer information, another argument for government intervention is to establish minimum quality standards for safety and efficacy (Malani and Philipson, 2012). One rationale is the fact that capturing the safety and efficacy of individual drugs and drug combinations imposes a substantial burden on consumers which has been exacerbated by the growth in the number of drugs available and insurance coverage. During the 1960s, the information burdens on consumers were relatively modest: there much fewer drugs available on the market and their quality were generally well-known. Since then, the number of drugs available on the market has greatly expanded, increasing the cost of processing information on drug quality. Further, the growth of insurance coverage for drugs may have encouraged individual consumers to be more price insensitive, dampening the incentives to avoid low quality drugs (Danzon and Keuffel, 2014).

Off-label use provides a useful setting in which to examine the central trade-off facing regulators of health care technologies: regulation must balance the benefits of information generation, safety, and efficacy, with the resource costs and lost patient benefits due to delay in access and fewer products. Former FDA Commissioner Margaret A. Hamburg and former Deputy Commissioner Joshua M. Sharfstein note that "as a public health agency, the FDA should always ask whether delays in approval or safety problems can be prevented"(Hamburg and Sharfstein, 2009). Given the high costs of generating clinical information on safety and efficacy, it is possible that regulation may have the perverse effect of lowering the amount of information generated. With sufficiently high clinical trial costs, manufacturers may choose against running clinical trials on new uses or may opt to conduct limited studies to generate off-label sales without ever intending to seek FDA approval (Eisenberg, 2005). Without formal evidence of safety and efficacy, physicians may inappropriately prescribe a drug or choose to avoid an appropriate therapy altogether.

4 Premarket Regulation and Off-Label Use

Before turning to empirical results, it is helpful to briefly outline the basic trajectory of the drug development and approval process. Current drug regulation is rooted in the 1938 Food and Drug Cosmetic Act(FD&C Act), which requires that manufacturers generate evidence of safety and efficacy as a pre-condition for marketing their products. Drug development typically begins with extensive preclinical laboratory research

23,000 ER visits were associated dietary supplements annually between 2004 and 2013.

that involves testing a new candidate on animals and human cells. Once complete, the manufacturer submits an Investigational New Drug Application (IND) to the FDA that outlines its plan of action with respect to human testing in clinical trials. After the IND is approved by the regulators, the manufacturer begins the most expensive aspect of drug development: human testing of drugs in a series of clinical trials in which costs increase with each subsequent phase. Drugs that successfully demonstrate safety in Phase I trials proceed to Phase II trials in which their efficacy is tested in a few hundred patients. If successful, the drugs move to Phase III trials in which their efficacy is tested in several thousand patients. Upon successfully completing the Phase III trials, the sponsor will submit a New Drug Application (NDA) to the FDA for final approval. The entire process is long (typically taking 8-12 years), costly (typically costing a manufacturer $800 million - $2.6 billion), and risky (only 9% of drugs that receive an IND ultimately go to market) (CSDD, 2014; Danzon and Keuffel, 2014; DiMasi, 2001; DiMasi et al., 2003).[4]

To expand a drug's label to include a new use, manufacturers must undertake additional clinical trials and submit a supplemental new drug application (sNDA). The amount of clinical trial evidence required may differ for NDAs and sNDAs. For instance, manufacturers seeking approval for new uses may skip the preclinical phase and rely on fewer phase 3 trials if the new indication is closely related to an approved use – e.g., a new phase of the same disease (FDA, 1998). With less evidence for the FDA to review, average approval times are shorter for sNDAs relative to NDAs (DiMasi, 2013; DiMasi et al., 1996; DiMasi and Lasagna, 1991). Despite this, the sNDA process is still considered expensive and time-consuming (Wittich et al., 2012). The evidentiary standards of safety and efficacy for original and supplemental indications are similar; an analysis of efficacy trials for approvals of sNDAs found that rates of use of active comparators and clinical outcome endpoints were comparable to those of trials supporting NDAs (Kesselheim and Wang, 2015). Further, firms typically must still run at least one phase 3 trial for which costs can run between $11.5 million to $52.9 million (Serkaya et al., 2016).

4.1 Premarket Regulation: Empirical Research

There is a large empirical literature that uses variation in premarket regulations to test for changes in investment decisions. The main advantage of this approach is the availability of large, exogenous FDA policy changes for study.

[4]These costs estimates reflect the direct cost of research and the opportunity cost of capital. The estimates have been subject to criticism due to small sample size, assumptions about the cost of capital, and the confidential nature of the underlying data (Avorn, 2015). Despite this, other efforts have generated similar cost estimates (Avorn et al., 2015).

4.1.1 Efficacy

The earliest studies examined changes in firm investments following the Kefauver Harris Amendments of 1962, which imposed proof-of-efficacy requirements.[5] This approach is rooted in the idea that efficacy standards might increase the costs of clinical development and lower incentives to produce of drugs of lower efficacy, changing the level and composition of future investments.

One of the first papers in this vein, Peltzman (1973), uses pre-1962 data to estimate a counterfactual model of new drug introductions and then inserts post-1962 data into his estimated model. The difference between the actual and predicted post-1962 new drug flows is attributed in the Peltzman study to the 1962 Amendments. He concludes that the costs of regulation reduced the annual flow of new chemical entities (NCEs), or chemical formulas not previously marketed, by more than 60% and that the 1962 Amendments led to a welfare loss in which associated decline in the introduction of new drugs – both ineffective and effective – outweighs the value of additional information.

The Peltzman paper has been highly influential and cited, but there is concern that the paper overestimates the impact of the 1962 in reducing the flow of new drugs (Carpenter, 2010). For example, Grabowski et al. (1978) suggest that the fall in NCE introductions was driven by other factors, such as diminishing returns in research productivity; the Thalidomide tragedy that may have increased manufacturer and physician risk aversion, hence reducing product demand; and pharmacologic advances which may have increased safety testing and R&D costs. The paper attempts to control for these possible confounding factors by comparing trends in NCE introductions in the US relative to the UK, which did not introduce testing for efficacy until 1971. The authors find that U.S. productivity –as measured by the number of NCEs per dollar of R&D– declined by six-fold compared to a threefold decrease in the UK and that this lower productivity was the attributable to the increased costs of regulatory compliance associated with the 1962 Amendments.

4.1.2 Review Times

A series of studies has examined the changes in approval times and research investments following the 1992 Prescription Drug User Fee Act (PDUFA), in which the FDA imposed user fees in exchange for a speedier review process. The motivating idea is that regulation that speeds up market access may lead to increased incentives to invest in research. While faster review times may not extend a drug's effective patent length (the Hatch-Waxman Act includes provisions restore patent time lost in FDA review), more rapid

[5]The Kefauver Harris Amendments largely define the regulations operating today. In addition to adding proof-of-efficacy requirements, the Amendments strengthened safety requirements and extended FDA regulation to cover clinical testing and manufacturing.

FDA approval can lead to gains in the present value of the manufacturer's return resulting from more time on market before technological or generic displacement (Vernon et al., 2006).

Evidence suggests that PDUFA significantly reduced review times for new drugs and increased investments. Using time series data between 1971 and 1998, Olson (2004b) finds that PDUFA reduced approval times of new molecular entity (NME), or molecular entities not previously marketed, by 34%. Consistent with this finding, Philipson et al. (2008) estimate that that NDA approval times fell about 9-10% annually between 1993-1997 and 5% annually between 1998 - 2002. Several researchers have examined the potential speed-safety trade-off associated with the PDUFA. Olson (2004a) finds that drugs granted expedited (i.e., "priority") review are associated with higher rates of post-launch reports of adverse drug reactions. However, Philipson et al. (2008) estimate that on net, the benefits to producers and consumers likely outweigh the costs of less-safe drugs. Vernon et al. (2006) is one of the few studies to directly examine the link between PDUFA and research investments. Consistent with the theory that faster approval times increases expected profitability, the authors estimate that a 10% decrease in approval times is associated with a 1.7% increase in R&D spending.

4.1.3 Supply-Side Policy Incentives

A sizable large literature examines supply-side policy incentives targeted towards increasing investments in conditions where no (or few) therapies exist because the cost of clinical trails likely exceed the expected returns to obtaining an additional FDA approval. Naturally, off-label use is common in these settings: physicians must rely on the use of drugs off-label when approved treatment options are limited or non-existent (e.g., Rituximab for Behcet's disease).

One of the FDA's most well known sets of incentives was created by the Orphan Drug Act of 1983 (ODA), which is designed to encourage the development of drugs for rare diseases (defined as diseases affecting fewer than 200,000 individuals). The ODA gives manufacturers the exclusive right to market a product ("marketing exclusivity") for seven years, tax credits for clinical research, and FDA advice throughout the development process. Using a difference-in-difference design, Yin (2008) finds that the ODA led to a 69% increase in the annual flow of new clinical trials for established rare diseases relative to a set of control diseases. In a follow-up study, Yin (2009) finds that half of the total R&D response to the ODA represents strategic indication-subdividing of non-rare diseases –i.e., firms strategically reducing their on-label market in order to quality for the ODA subsidy. Interestingly, this suggests that an off-label strategy may be profitable especially with the ODA benefits and that the ODA may have led to an increase off-label use.

Another program aimed at increasing incentives to generate additional information on drugs is the FDA's

1997 pediatric exclusivity provision.[6] Prior to 1997, nearly 75% of pediatric prescriptions were off-label due to the high cost of conducting clinical trials in children and the low expected profits of obtaining subsequent drug approval for use specifically in pediatric popuations.[7] In response, Congress enacted a provision which provides six months of patent or marketing exclusivity for approved drugs in return for conducting pediatric studies.[8] Li et al. (2007) examine clinical trials of nine drugs granted pediatric exclusivity and estimate the economic return for performing the additional trials and receiving six months of exclusivity ranged from approximately -$9 million to $507 million. Since the 1997 provisions, the number of trials for use in pediatric populations increased following the 1997 provisions (Kesselheim, 2011). Olson and Yin (2016) provide evidence that this partly reflects a strategic response by firms to maximize the profit potential of the additional exclusivity: firms conduct pediatric studies in drugs with large adult and pediatric markets, rather than drugs treating diseases with greater prevalence in children.

Lastly, the FDA grants successful sNDA applicants three years of marketing exclusivity. However, the benefits to this incentive are limited: generic manufacturers can simply promote off-label uses of their own products.

5 Advertising and Off-Label Use

Despite the information elicited through the approval process, there remain substantial uncertainty about the safety and efficacy of an approved drug – particularly for uses that were not approved and for which information on safety and efficacy is preliminary or unavailable. For instance, clinical trials are often conducted for specific uses on a narrow population within a limited time frame. Consequently, the long-term safety of the drug in non-designated populations may not yet established upon drug approval. To the extent that manufacturers have additional information not included on the drug's label, promotion by manufacturers is an important means by which physicians, consumers, and payers learn about the drug's safety and efficacy.[9] However, regulators concerned that research outside of the FDA's control is less rigorous and that the information disseminated from such trials may pose a public health risk(FDA, 2014). Indeed, it's well established that industry sponsored-clinical trials tend to report larger treatment effects relative to comparable non-industry sponsored trials (Bekelman et al., 2003). As a result, the FDA aims to dissuade firms from avoiding the regulatory approval process by bands the direct promotion of drugs, arguing that doing

[6] Additional regulatory exclusivities include those for new molecular entities, additional clinical trials on existing drugs, and pediatric uses.

[7] http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143565.htm

[8] The pediatric exclusivity provision was reauthorized and strengthened (from voluntary to mandatory) through the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

[9] While direct-to-consumer advertising (DTCA) has expanded in the past two decades, direct-to-physician advertising continues to be the primary form of advertising. Iizuka (2004) provides more detail.

so would violate the provisions of the FD&C Act which prohibits the introduction of "misbranded" drugs.

Despite restrictions on directly promoting off-label uses, manufacturers of approved drugs continue to view promotion as an effective strategy for increasing sales (Scott Morton and Kyle, 2012). Using a difference-in-difference specification and prescribing data from IMS Health, Larkin et al. (2014) estimate that policies restricting the direct promotion of drugs to physicians via visits or sales calls ("detailing") at academic medical centers led to a 11% drop in off-label use of antidepressants and antipsychotics in children, which suggests the presence of off-label marketing to physicians.[10] Moreover, the FDA's stance towards off-label advertising has since been successfully loosened and challenged. Manufacturers are currently permitted to respond to unsolicited questions about off-label uses from health care professionals and to disseminate information describing off-label uses from a variety of sources, including textbook chapters, clinical practice guidelines, and peer-reviewed journal articles(Avorn et al., 2015; FDA, 2014). Recent legal decisions concluding that the dissemination of truthful information about unapproved uses constitutes freedom of speech bolsters the persistence of off-label promotion.

5.1 Advertising: Empirical Research

Many researchers have studied the effects of physician detailing on prescribing behavior. This research is motivated by the fact that pharmaceutical advertising can impact demand through providing additional information ("informative effect") or altering tastes and preferences ("persuasive effect") (Dave, 2013). Under the informational view, manufacturers can raise awareness of new uses of existing drugs, as well transmit information on product attributes which can help physicians assess the quality of a potential drug-patient match. Under the persuasive view, additional advertising serves primarily to maintain brand affinity. Dave (2013) argues that the different views of advertising are not mutually exclusive – as a product moves through its life cycle, advertising may evolve from having an informational to persuasive intent.

There are several empirical challenges associated with measuring how prescribing behavior changes in response to detailing effort (i.e., the detailing elasticity). First, few researchers have been able to successfully separate the information effects from the promotional effects (Scott Morton and Kyle, 2012). Second, detailing is often individually targeted, resulting in estimates that are biased upwards. To address this challenge, researchers have used a variety of approaches. Using an instrumental variable approach, Berndt et al. (1995) use data on detailing minutes and number of pages of medical journal advertising for branded anti-ulcer drugs. They estimate that demand elasticities for detailing (0.55) exceed those of journal advertising (0.20) concluding that physician-directed marketing is most effective at shaping prescribing behavior. Using

[10] Recent lawsuits involve Eli Lilly and Co. ($1.4 billion in 2009); GlaxoSmithKline ($3 billion in 2012); Abbott ($1.6 billion in 2012); Pfizer ($2.3 billion in 2009).

physician fixed effects models, Datta and Dave (2013) examine how the number of prescriptions of the drug, Famvir, change in response to the level of "detailing stock" (which if a function of the current and previous month's detailing) and estimate elasticities of 0.05 to 0.07. These smaller estimates suggest that previous studies may have resulted in estimates that reflect unobserved selection. These effects are largely driven by new users (i.e., an extensive margin) as opposed to existing users (i.e., an intensive margin). Finally, Shapiro (2015) is one of the few studies that explicitly examines the impact of detailing on off-label behavior. Using a detailed panel of physician visits, he finds a small impact of physician detailing on off-label prescribing in the anti-psychotic category, though this is far outweighed by the detailing effects on on-label prescribing.

In contrast to the literature on estimating detailing elasticities, the literature on the advertising and regulation is sparse. David et al. (2010) is one of the few studies to highlight how the threat of regulatory action (e.g., labeling changes to reflect black box warnings, warnings, precautions) may shape firms' off-label advertising decisions. Specifically, the authors examine whether manufacturers advertising decisions are limited by the increase risk of low quality patient-drug matches which can lead to regulatory actions against the firm. Using data on pharmaceutical promotion, FDA regulatory actions, and adverse drug reactions (ADRs), the authors find among drugs used to treat arthritis pain, a one standard deviation increase in detailing expenditures raises ADR reporting by 60 percent and 100 additional ADRs increase the probability of regulatory action by one percentage point.

6 Data Sources

Off-label use provides a fertile area to explore questions related to the role of information for clinical decision making, and the role of regulation in shaping the production and dissemination of information about the quality of new health care technologies. For researchers interested in this area, the following resources provide a good starting point:

- Original and Supplemental Drug Approvals: Drugs@FDA
  - Note: this does not include all biologics
- Evidence of Off-label Uses:
  - Scientific literature: PubMed
  - Compendia (subscriptions required):
    - American Hospital Formulary Service Drug Information (AHFS-DI)
    - Clinical Pharmacology

        * National Comprehensive Care Network (NCCN)
        * DRUGDEX
    - Clinical trials:
        * Clinicaltrials.gov
        * Pharmaprojects (subscription required)
        * Thomson Reuters Cortellis (subscription required)
    - Adverse events reporting:
        * FDA Adverse Event Reporting System (FAERS)
        * FDA MedWatch Safety Alerts
        * FDA Drug Safety Labeling Changes
- Pharmaceutical Advertising: IMS Health (subscription required)

References

Adams, Christopher P. and Van V. Brantner. 2006. "Estimating The Cost of New Drug Development: Is it Really $804 Million?" Health Affairs 25(2):420-428.

Agha, Leila and David Molitor. 2015. "The Local Influence of Pioneer Investigators on Technology Adoption: Evidence from New Cancer Drugs." NBER Working Paper No. 20878.

Akerlof, George A. 1970. "The Market for 'Lemons': Quality Uncertainty and Market Mechanism." The Quarterly Journal of Economics 84(3): 488-500.

Avorn, Jerry. 2015. "The $2.6 Billion Pill – Methodologic and Policy Considerations." NEJM 372:1877-1879.

Avorn, Jerry, Ameet Sarpatwari, and Aaron S. Kesselheim. "Forbidden and Permitted Statements about Medications - Loosening the Rules." NEJM 373:967-973.

Bekelman, Justin E., Yan Li, and Cary P. Gross. 2003. "Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review." JAMA 289(4):454-465.

Berndt, Ernst R., Linda Bui, David R. Reiley, Glen L. Urban. 1995. "Information, Marketing, and Pricing in the U.S. Antiulcer Drug Market." The American Economic Review 85(2): 100-105.

Bradford, W. David, John L. Turner, and Jonathan W. Williams. 2014. "Off-Label Use of Pharmaceuticals: Trends and Drivers." Working Paper.

Carpenter, D.P. 2010. Power Reputation Organizational Image and Regulation at the FDA. Princeton University Press: Princeton.

Conti, Rena M., Arielle C. Bernstein, Victoria M. Villaflor, Richard L. Schilsky, Meredith B. Rosenthal, and Peter B. Bach. 2013. "Prevalence of Off-Label Use and Spending in 2010 Among Patent-Protected Chemotherapies in a Population-Based Cohort of Medical Oncologists." Journal of Clinical Oncology 31: 1-6.

Tufts Center for the Study of Drug Development (CSDD). 2014. "Costs to Develop and Win Marketing Approval for a New Drug is $2.6 Billion." http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

Danzon, Patricia M. and Eric L. Keuffel. 2014. "Regulation of the Pharmaceutical-Biotechnology Industry." In Economic Regulation and Its Reform: What Have We Learned?, edited by Nancy L. Rose, 407-484. Chicago: University of Chicago Press.

Datta, Anusata and Dhaval M. Dave. 2013. "Effects of Physician-Directed Pharmaceutical Promotion of Prescription Behaviors: Longitudinal Evidence." NBER Working Paper 19592.

Dave, Dhaval M. 2013. "Effects of Pharmaceutical Promotion: A Review and Assessment." NBER Working Paper 18830.

David, Guy, Sarah Markowitz, and Seth Richards-Shubik. 2010. "The Effects of Pharmaceutical Marketing and Promotion on Adverse Drug Events and Regulation." American Economic Journal: Economic Policy 2 1-25.

DiMasi, Joseph A. 2001. "New Drug Development in the United States." Clinical Pharmacology and Therapeutics 69(5):286-296.

DiMasi, Joseph A. 2013. "Innovating by developing new uses of already-approved drugs: trends in the marketing approval of supplemental indications." Clinical Therapeutics 35(6):808-818.

DiMasi, Joseph A. and Louis Lasagna. 1991. "Development of supplemental indications for already approved drugs by the United States pharmaceutical industry." Journal of Clinical Research and Pharmacoepidemiology 5(1):19-33.

DiMasi, Joseph A., Jeffery S. Brown, and Louis Lasagna. 1996. "An analysis of regulatory review times of supplemental indications for already-approved drugs: 1989 to 1994." Therapeutic Innovation & Regulatory Science 30(2):315-337.

DiMasi, Joseph A., Ronald W. Hansen, and Henry G. Grabowski. 2003. "The Price of Innovation: New Estimates of Drug Development Costs." Journal of Health Economics 22 (2): 151–85.

Dranove David and Ginger Zhe Jin. 2010. "Quality Disclosure and Certification: Theory and Practice." Journal of Economic Literature 48(4): 935-963.

Eisenberg, Rebecca S. 2005. "The Problem of New Uses." Yale Journal of Health Policy, Law, and Ethics 5(2): 717-740.

FDA. 1998. "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products."

FDA. 2014. "Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices."

Friedman, Michael. 1996. "Testimony on Supplemental Indications for Approved Prescription Drugs." House Committee on Government Reform and Oversight, Subcommittee on Human Resources and Intergovernmental Relations.

Geller, Andrew I., Nina J. Weidle, Beverly J. Wolpert, and Robert P. Mozersky. 2015. "Emergency Department Visits for Adverse Events Related to Dietary Supplements." NEJM 373:1531-40.

Grabowski, Henry G., John M. Vernon, and Lacy Glenn Thomas. 1978. "Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Pharmaceutical Industry." The Journal of Law and Economics 21(1): 133-163.

Hamburg, Margaret A. and Joshua M. Sharfstein. 2009. "The FDA as a Public Health Agency." NEJM 360: 2493-95.

Iizuka, Toshiaki. 2004. "What Explains the Use of Direct-to-Consumer Advertising of Prescription Drugs?" The Journal of Industrial Economics 52(3): 349–379

Katz, Ariel. 2007. "Pharmaceutical Lemons: Innovation and Regulation in the Drug Industry." Michigan Telecommunications and Technology Law Review 14(1):1-41.

Kesselheim Aaron S. 2011. "An Empirical Review of Major Legislation Affecting Drug Development: Past Experiences, Effects, and Unintended Consequences." The Milibank Quarterly 89: 450-502.

Kesselheim, Aaron S. and Bo Wang. 2015. "Characteristics of Efficacy Evidence Supporting Approval of Supplemental Indications for Prescription Drugs in United States, 2005-14: Systematic Review." BMJ 351:h4679

Larkin, Ian, Desmond Ang, Jerry Avorn and Aaron S. Kesselheim. 2014. "Restrictions on Pharmaceutical Detailing Reduced Off-Label Prescribing of Antidepressants and Antipsychotics in Children." Health Affairs 33(6):1014-1023.

Lee, Euni, Anna R. Teschemaker, Rosemary Johann-Liang, Gina Bazemore, Martin Yoon, Kye-Sik Shim, Marlon Daniel, Jerome Pittman, and Anthony K. Wutoh. 2012. "Off-Label Prescribing Patterns of Antidepressants in Children and Adolescents." Pharmacoepidemiology and Drug Safety 21:137-144.

Li, Jennifer, Eric L. Eisenstein, Henry G. Grabowski, Elizabeth D. Reid, Barry Mangum, Kevin A. Schulman, John V. Goldsmith, M. Dianne Murphy, Robert M. Califf, and Daniel K. Benjamin. 2007. "Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program." JAMA 297(5):480-488.

Malani, Anup and Tomas J. Philipson. 2012. "The Regulation of Medical Products." In The Oxford Handbook of the Economics of the Biopharmaceutical Industry, edited by Patrica M. Danzon and Sean Nicholson, 100-142. New York: Oxford University Press.

Molitor, David and Leila Agha. 2012. "Technology Adoption Under Uncertainty: Off-label Prescribing in Cancer Care." Dissertation Chapter.

Nelson, Philip. 1970. "Information and Consumer Behavior." Journal of Political Economy 78(2):311-329.

Olson, Mary K. 2004a. "Are Novel Drugs More Risky for Patients than Less Novel Drugs?" Journal of Health Economics 23(6):1135-58.

Olson, Mary K. 2004b. "Managing Delegation in the FDA: Reducing Delay in New-Drug Review." Journal of Health Politics, Policy, and Law 29(3): 397-430.

Olson, Mary K and Nina Yin. 2016. "Examining Firm Responses to Innovation Policy: An Analysis of Pediatric Exclusivity." Working Paper.

Peltzman, Sam. 1973. "An Evaluation of Consumer Protection Legislation: the 1962 Drug Amendments." Journal of Political Economy 81(5): 1049-1091

Philipson, Tomas J., Ernst R. Berndt., Adran H. B. Gottschalk, Matthew W. Strobeck. 2008. "Assessing the Safety and Efficacy of the FDA: The Case of the Prescription Drug User Fee Acts." NBER Working Paper 11724.

Radley, David C., Stan N. Finkelstein, Randall S. Stafford. 2006. "Off-Label Prescribing Among Office-Based Physicians." JAMA Internal Medicine 166(9):1021-1026.

Roin, Benjamin. 2013. "Solving the Problem of New Uses."

Scott Morton, Fiona and Margaret Kyle. 2012. "Markets for Pharmaceutical Products," In Handbook of Health Economics, Vol. 2, edited by Mark V. Pauly, Thomas G. Mcguire and Pedro P. Barros, 763-823. Amsterdam: Elsevier Science.

Sertkaya, Aylin, Hui-Hsing Wong, Amber Jessup, and Trinidad Beleche. 2016. "Key Cost Drivers of Pharmaceutical Clinical Trials in the United States." Clinical Trials 13(2): 117-126.

Shapiro, Bradley T. 2015. "Informational Shocks, Off-Label Prescribing, and the Effects of Physician Detailing." Working Paper.

Stafford, Randall S. 2008. "Regulating Off-Label Drug Use –Rethinking the Role of the FDA." NEJM 358(14):1427-1429.

Vernon, John A., Joseph H. Golec, Randall Lutter, and Clark Nardinelli. 2006. "FDA New Drug Approval Times, Prescription Drug User Fees, and R&D Spending." Working Paper.

Wittich, Christopher M., Christopher M. Burkle, and William L. Lanier. 2012. "Ten Common Questions (and Their Answers) About Off-label Drug Use." Mayo Clinic Proc 87(10):982-990.

Yin, Wesley. 2008. "Market Incentives and Pharmaceutical Innovation." Journal of Health Economics 27: 1060-1077.

Yin, Wesley. 2009. "R&D Policy, Agency Costs, and Innovation in Personalized Medicine." Journal of Health Economics 28: 950–962.