How Do Restrictions on Advertising Affect Consumer Search?

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Abstract

Advertising is often criticized for presenting only partial or selective information about products. This criticism is particularly pronounced for health products, where large asymmetries in information may exist between consumers and firms. This paper explores how government restrictions designed to prevent selective advertising affect the types of information to which consumers are exposed. We exploit a natural experiment in the form of an FDA crackdown that prevented pharmaceutical companies from using selectively chosen information in their Internet search ads. Since companies could not adequately document side-effects within the advertising space allowed, they removed their ads. Our results suggest that, after the ads were removed, consumers were more likely to seek information from websites based on user-generated content or websites that focused on medical treatments not regulated by the FDA, such as Canadian pharmacies and sites promoting herbal remedies.

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1 Introduction

When designing ads, companies select which information to provide to consumers. Selective information may be undesirable if large asymmetries exist between consumers and firms regarding a product's quality or risks. To protect consumers against ads with misleading or incomplete information, regulators in the health and financial sectors often require ads to disclose fully any potential risks associated with the product. This paper investigates how prohibiting or removing ads with selectively-chosen information affects consumer behavior.

We examine whether consumers respond to such ad removal by seeking information from other sources, and if so, whether these alternative sources are more reliable. To investigate this empirically, we exploit a shift in enforcement policy initiated by the US Food and Drug Administration (FDA) regarding pharmaceutical advertising. On March 26, 2009, the FDA issued notices to the manufacturers of 48 drugs, stating that their online ads on search engines did not convey any risk information and therefore contravened existing regulations on pharmaceutical advertising. Since search ads have a limit of three lines of text, many pharmaceutical companies could not adequately document the side-effects and consequently removed their ads. Industry estimates suggest that the number of pharmaceutical ads fell by 84 % immediately after the ruling (Staton, 2009). The FDA's enforcement action allows us to study consumers' response to regulation, and it also sheds light on an industry that is highly regulated and devotes significant resources to advertising.

We examine the change in consumer behavior on major search engines from February to June 2009, the period before and after the FDA issued warning letters. Since search ads provide information in direct response to a consumer's query for new information, this data provides an opportunity to study the effects of advertising on consumer search. Our data derives from monthly data of aggregated search queries and the subsequent websites searchers visited. We investigate consumer searches associated with the drugs targeted by the FDA

and the medical conditions and symptoms they treat (e.g., "breast cancer," "hair loss"). To provide a baseline trend for health searches, we also use searches on medical devices used to treat those conditions. Medical devices are not subject to the same requirements as pharmaceutical drugs for the disclosure of side-effects. However, medical devices should be subject to the same shifts in underlying demand for medical information as pharmaceutical products.

Our results demonstrate that after the FDA imposed restrictions to prevent partially-informative advertising, consumers clicked on different sources of information. Estimates indicate that consumers may be more likely to seek information from unverified sources, including advertisers not regulated by the FDA, such as sites promoting herbal remedies or non-US-based pharmacies, as well as sources that contain user-contributed information such as forums. If so, consumers were more likely to seek information from these sources rather than official sources, such as government or non-profit organizations.

Searches for information and conditions are typically "non-navigational" as opposed to searches for a predetermined destination (Blake et al., 2015). To check that our results reflect the fact that searchers for conditions did not have a predetermined destination in mind and therefore were more likely to be influenced by website advertising, we compare our results to more "navigational" searches where a customer searched on a specific pharmaceutical brand and was more likely to be trying to reach a predetermined destination (Bechtold and Tucker, 2014). We find some evidence that consumers who searched a brand name of a drug were less affected by the FDA enforcement action. One explanation is therefore such customers had a navigational purpose in using the search engine, rather than using it to find possible information sources.

This paper builds on a prior literature that investigates how advertising bans or restrictions affect sales in industries such as cigarettes (Laugesen and Meads, 1991; Saffer and Chaloupka, 2000; Stewart, 1993), alcohol (Saffer, 1997; Nelson, 2003; Goldfarb and Tucker,

2011a), pharmaceuticals (Boscaljon, 2005), and legal services (Goldfarb and Tucker, 2011b). The novelty of our paper is that we study how restrictions on advertising affect which types of information consumers seek. Our paper also relates to previous studies on the role of direct-to-consumer pharmaceutical advertising on consumers' treatments and check-ups as well as manufacturer market expansions (Iizuka and Jin, 2005; Wosinska, 2005; Donohue, 2006; Calfee et al., 2002; Narayanan et al., 2004; David et al., 2010). To our knowledge, this paper is the first to document the role that restrictions on advertising have on the set of information that a potential patient initially gathers about a pharmaceutical product.

Regulation that is designed to constrain advertisers from giving selectively information is intended to ensure that consumers receive comprehensive and balanced information. However, our findings imply that regulation of selectively informative ads may lead to unintended consequences for consumer behavior, given the availability of alternative sources of information. Our results illuminate the difficulties of applying existing rules designed for offline advertising (where consumers are often passive recipients of ads) to online advertising (where consumers are actively seeking information). In such environments, regulators need to consider what alternative sources of information consumers may substitute towards after advertising is restricted.

Our findings are also useful in describing marketing outcomes when firms do not advertise. The results suggest that in specific instances, paid search advertising on a search engine may not be necessary if a consumer already searches with a brand name and consequently may be performing a navigational search. This is consistent with initial evidence by Blake et al. (2015), who used field experiment data from eBay to show that paid search ads targeted at the trademark eBay simply substitute for non-paid clicks and therefore offer a negative return on investment. This result contradicts earlier findings of complementarities between paid search and organic search outcomes (Yang and Ghose, 2010). Our paper provides a bridge between these two contradictory findings, since we find evidence of substitution for

brand name searches, but some evidence of complementarities between paid search ads and organic search clicks when the searcher searches for a medical condition or symptom.

2 The FDA Ruling

The Food and Drug Administration (FDA) has regulated prescription drug advertising since 1962. The FDA's actions in recent years reflect increasing attention towards the regulation of direct-to-consumer advertising as opposed to physician advertising. As pointed out by Donohue et al. (2007), the proportion of promotion-related regulatory letters citing problems with direct-to-consumer advertisements (as opposed to promotional material aimed at health professionals) increased from 15.5% of all letters in 1997 to 33.3% in 2006. A study in 2013 of trends of enforcement letters suggested that the presentation of risk information—the issue in the policy action we study—was the focus of 68.4% of enforcement letters. While the number of letters has declined over the past decade, focus on presentation of risk information has increased (Limbu et al., 2019).

However, the increase in FDA attention to direct-to-consumer advertising focused on traditional media channels such as television and print media. How the existing regulations would be applied or ought to be interpreted for new channels such as social media or search advertising was unclear. Indeed, the FDA announced in September 2009 that it was holding a two-day hearing on how pharmaceutical companies were using the Internet and online social-media networks to market their products. The FDA was aware that "emerging technologies may require the agency to provide additional guidance to the industry on how the regulations should be applied." In the same statement, the FDA highlighted that the last time it had issued clarification on the issue of pharmaceutical company presence or advertising on the Internet was in 1996.[1]

[1]The FDA-issued materials from 1996 were unlikely to be helpful to pharmaceutical companies trying to understand how regulation would apply to search advertising. When describing hyperlinks, one of its presentations stated that "Hyperlinks are..little blue text items. If you've ever been on a Web page, you see those little things highlighted in blue." This lack of guidance is unsurprising, however, given that by 1996

The ambiguity in policy changed on March 26, 2009 when the FDA issued letters of warning to 14 major pharmaceutical companies, regarding their Internet ads that accompanied keyword searches on Google and other search engines. The FDA indicated in its press release that its concerns were motivated by the severity of the potential side-effects associated with these drugs. It stated that the ads were misleading because they did not include information on the risks or side-effects associated with a drug. These warnings were one of the first major actions by the FDA to crackdown on Internet promotions. The companies that received letters were Biogen, Sanofi-Aventis SA, Johnson & Johnson, GlaxoSmithKline PLC, Forest Laboratories Inc., Cephalon Inc., Bayer AG, Novartis AG, Merck & Co., Eli Lilly & Co., Pfizer, Roche Holding AG, Genentech Inc. (now acquired by Roche), and Boehringer Ingelheim Pharmaceuticals Inc. Nineteen of the 48 drugs cited in the letters carry a black box, which is the FDA's strongest warning on possible side-effects.[2]

A typical FDA letter resembled the one sent to Hoffmann-La Roche, regarding its drugs Boniva, Pegasys, and Xeloda. We quote the full text of the letter in the Appendix to this article. The letter cited ads that had the message, "XELODA Information www.xeloda.com Learn About An Oral Chemotherapy Treatment For Colon Cancer." The FDA criticized these ads, saying "By omitting the most serious and frequently occurring risks associated with the drugs promoted in the links above, the sponsored links misleadingly suggest that Boniva, Pegasys and Xeloda are safer than has been demonstrated." Even though the ad included a link to the website for the drug, which did contain the relevant risk information, the FDA said the link was "insufficient to mitigate the misleading omission of risk information from these promotional materials." The FDA gave the company until April 9, 2009 to prove compliance.

paid search advertising had not yet evolved.

[2]FDA Warns Drug Firms Over Internet Ads, Wall Street Journal, April 4, 2009.

3 Data

We obtain data on search advertising and consumer online behavior from comScore's Search Planner database.[3] This database reports the average click behavior of consumers following a keyword search on any of the three major search engines. For each keyword search, comScore reports the monthly aggregate number of clicks received by a website either through a "paid" link or a "non-paid" link.

When a user conducts a keyword search for a pharmaceutical product, the search engine returns a list of results containing links to several different websites. Some of the links are from advertised sources ("paid links") while others are from non-advertised sources ("unpaid links"). For instance, Figure 1 depicts the search results from a query on the keyword of the drug "Levitra" using the Google search engine. The search engine displays a list of paid links in the sponsored results section (at the top and to the right) of the search results page as well as a separate list of non-paid links within the body of the main search results. Advertisers bid for the paid links, which are text ads that appear in response to consumers' keyword searches. When a user clicks on the paid link, the advertiser must pay the search engine. A website can sometimes appear in both the sponsored and main results page. For instance, in Figure 1, the product website for Levitra (www.levitra.com) appears both as a paid link in the sponsored results section and also as a non-paid link within the main search results. Note that the FDA warning targeted the paid links or search ads by pharmaceutical companies. In addition to pharmaceutical companies, many different types of advertisers place ads on keywords containing a pharmaceutical brand name or medical condition. For instance, most

[3]ComScore tracks the online activity of a panel of more than 2 million users based in the US and subsequently aggregates their search patterns to the search-term level for resale to commercial clients. ComScore recruits its panel members through affiliate programs and partnering with third party application providers. ComScore emphasizes and discusses the representativeness of their sample to the general population in their Marketer User Guide. The comScore data has also been used in several academic studies and noted as a "highly regarded proprietary [source] for information on the size and composition of media audiences" (Gentzkow and Shapiro, 2011; Montgomery et al., 2004; De Los Santos et al., 2012).

ads for the keyword "Levitra" are either for online pharmacies (often Canadian) such as northwestpharmacy.com or kwikmed.com, or for alternative natural remedies for erectile dysfunction like zernerx.com. These sites are able to advertise because no legal restriction exists on bidding for a pharmaceutical brand name.[4]

Since a vast set of combinations of search terms and websites exist, comScore imposes some selection criteria for inclusion into its database. ComScore only collects data on specific phrases that arise from queries by at least two different panel members. Under its minimum reporting standards, comScore does not record the number of clicks for websites that receive clicks from fewer than three unique users but instead reports them simply as having been visited at least once. We assume that such websites receive two clicks.[5]

3.1 Types of Keywords

We collect information on keyword searches for medical conditions and symptoms associated with the targeted products. We identify the top two medical condition and symptom phrases that were used by consumers to navigate to a pharmaceutical website in February 2009, where such data was available. The medical conditions include terms such as "breast cancer" and "hypertension." These keyword terms align closely with the medical conditions mentioned in the FDA warning letters. Table A-2 contains a list of the 61 keywords for the corresponding medical conditions within our sample. Some overlap of medical conditions occurs among the targeted drugs.[6]

To provide a baseline for any change in health-related searches, we also collect data on keyword searches on medical devices. For example, if a patient has "erectile dysfunction," they may search for a drug like "Viagra," or they may search for a treatment based on a

[4]In *Merck & Co. v. Mediplan Health Consulting, 2006 WL 800756 (SDNY Mar. 30, 2006)*, the court dismissed Merck's claims of infringement on the grounds that Mediplan's search advertising on keywords such as "Zocor" did not represent a use of a trademark in commerce.

[5]Our main results are robust to assuming such websites receive only one click.

[6]The drugs Bystolic, Diovan, and Exforge treat hypertension. Avandmet, Avandia, and Januvia treat diabetes.

medical device such as a "penile implant." Similarly, a patient who has "heart disease" could search for one of the drugs in our sample or for a "home blood pressure monitor." We collect this data because our identification strategy relies on changes in search outcomes correlated with the change in FDA enforcement and not with another contemporaneous change in health-related searches.

The identifying assumption is that consumers' searches on medical devices will reflect general trends in health searches, but the FDA warning will not affect searches on medical devices. This is because "unlike the direct-to-consumer advertising of drugs, direct-to-consumer advertising of medical devices has not yet been highly scrutinized" (O'Riordan, 2008). We identify medical devices mentioned by the Mayo Clinic website in its description of the treatment for the medical conditions in our sample. Table A-3 of the Appendix lists the device keywords.[7]

We also collect information on keyword searches that contained the brand name for each of the 48 pharmaceutical products targeted by the FDA. Our dataset includes keyword searches containing 33 drugs that were targeted by the FDA. For the remaining 15 drugs, comScore did not observe enough panelists visiting their websites through a brand name search to record click activity. These drugs were Aromasin, Avandaryl, Emend, Evista, Exjade, Fentora, Lucentis, Pegasys, Prezista, Pulmozyme, Treanda, Tykerb, Tysabri, and Xolair. It is likely that the low number of visits by users is due to the narrowness of the conditions the drugs treated.

In the Appendix, Table A-1 contains the list of brand name keywords in our sample. For each of the targeted drugs, the table lists the medical conditions that the drug treats, major side-effects and treatment protocols, and the product webpage. We use brand name searches as a robustness check in section 4.2.

[7]Some medical devices did not receive enough searches to appear within the database—e.g., "aneurysm clip," "emobilization device."

3.2 Types of Websites

We observe the sites that consumers clicked after searching the keywords discussed above. Given this set of sites, we classify each website into one of five disjoint categories using the following procedure. We identify the websites of the products and pharmaceutical companies that were targeted by the FDA letters. For instance, Bayer (the manufacturer of Levitra) maintains the product website levitra.com as well as its own manufacturer website www.bayer.com. We include both types of sites within this category and refer to them as "pharmaceutical websites." In cases where a single product had two websites (e.g., Yaz.com and Yaz-US.com), we include data for both websites in our sample.

Next, we identify websites that promoted medical solutions that are either prohibited by the FDA or that are not subject to strict control and testing by the FDA. We refer to these sites collectively as "non-regulated websites," and they fall into three main groups. The first are websites such as discountdrugsfromcanada.com that allow consumers to order prescription medications from outside of the US. US Federal law prohibits consumers obtaining prescription drugs from Canada where they are cheaper due to government price caps, because of safety concerns over whether the drugs are genuine or fake. Bate et al. (2013) used Raman spectrometry to analyze physical samples of drugs ordered from pharmacies. They found that orders from non-American pharmacies that were certified by an external body such as PharmacyChecker or Canadian Internet Pharmacy Association (CIPA), which requires the website to mandate prescriptions, had no instances of supplying drugs with incorrect ingredients. For the other websites that were not certified, the ingredients of the drugs analyzed did not prove authentic in some cases. In our data, 8 out of 170 pharmacy websites were certified by one of the certifying authorities identified by Bate et al. (2013), though, as the paper also points out, this certification may not be meaningful.

The second group of non-regulated websites consists of websites that offer herbal remedies

such as nativeremedies.com. Although homeopathic remedies are regulated by the FDA, they do not have to undergo the same testing and review by the FDA before being sold as pharmaceutical products do. These manufacturers are not subject to the same fair-balance requirements in advertising as pharmaceutical products.

The third group of non-regulated websites offers advice about the consumption of marijuana, such as weedsthatplease.com. At the time, thirteen states approved the use of marijuana for medical purposes, but the FDA had not approved a medical use for marijuana.

Then, we identify sites as "user-generated content" (UGC) if their URLs contained the words "community," "groups," "answers," or "forum." We also include websites that allowed users to pose questions, which are then answered by other community members, such as "Yahoo! Answers." This categorization defines a set of websites where information is provided by members of the public rather than by verified or official sources. Given the FDA's emphasis in its letters on ensuring that information was complete and balanced, such websites do not necessarily fulfill this role. However, we do emphasize that the role of user-generated in content and its helpfulness in spreading accurate information is subject of academic inquiry and debate (Moorhead et al., 2013).

For the remaining websites, we use the suffix of their URL to divide them into two additional categories: "non-profit" and "commercial." We identify websites as "non-profit" if the website address contained a suffix of .ORG, .EDU, or .GOV, and we identify websites as "commercial" if they did not contain either of these suffixes. The motivation behind classifying "non-profit" sites is to delineate a set of websites that are more likely to provide impartial, balanced, and educational information because of their governmental or non-profit status.

The commercial websites include websites, such as www.webmd.com, that specifically provide medical content and may be supported by revenues from advertising. This category also includes more general sources of information that may feature health-related news or

products, such as associatedcontent.com, as well as the websites of pharmaceutical products and manufacturers that were not targeted by the FDA.

The final category of websites in our data is search websites. This category captures the behavior of consumers who were dissatisfied with the search results and returned to the search engine to perform a different search. We refer to this behavior as terminating that search and treat it as the "outside" option in our empirical specifications. Given the way comScore data is constructed, we do not observe details on people who completely stop searching after seeing a set of search results. This occurs because the comScore data are focused on searches and online navigation rather than termination.

To summarize, the categories of websites described above are mutually exclusive and exhaustive of the sites we observe in our sample. The categories include pharmaceutical, non-regulated, user-generated content, non-profit, and commercial. The outside option is terminating the current keyword search by performing a different keyword search.[8]

3.3 Final Sample

Our final sample contains the number of total, paid, and non-paid clicks received by each website for keyword searches at the monthly and search engine level. The data span the period from February 2009 to June 2009. Our data captures online behavior on the three major search engines—Google, Live (Bing) and Yahoo!. As an example of an observation within our sample, we observe the total number of total, paid and non-paid clicks received by www.levitra.com from users who conducted a keyword search containing "Levitra" from Google during June 2009.

The initial dataset on medical conditions and symptoms includes 13,016 combinations of keyword and websites subsequently visited by consumers, totalling 52,064 observations over four months. Some overlap of websites occurs across search terms; for example, webmd.com

[8]For our sample of medical devices, we do not observe any paid or non-paid clicks to the targeted pharmaceutical companies, which is not surprising given that a search for a device is unlikely to lead to a visit to a pharmaceutical company.

received clicks from searches on pharmaceutical brands as well as medical conditions and symptoms. In sum, our panel data contains information on search terms used to reach 3,286 unique websites.

Table 1 reports summary statistics for our panel of website and search combinations. Most of the clicks to the websites originated from non-paid links. The average website in our sample received 1,542 total clicks, of which 1,422 were non-paid. Pharmaceutical websites comprise a small fraction of the sample of website and search combinations (1.2%). The relatively small proportion may exist because we obtain data for searches relating to broad medical conditions like diabetes—it seems natural that only a small percentage of these searches would theoretically ever result in a visit to a pharmaceutical webpage. Non-regulated sites consist of a similar fraction of the sample (1.1%). UGC sites were more prevalent in the sample (2.1%). Non-profit websites are 23% of the sample. Commercial websites which span other unclassified sites were 68% of this sample whereas the baseline behavior of terminating a search occurred 3.1% of the time.

One issue with examining the data at the search-term level is that some popular websites such as webmd.com are counted multiple times in this sample, since they are reached through different keyword searches. Table 2 reports the data at the website-level. When we examine the summary statistics of the 3,286 websites over the four-month period, we see similar patterns as Table 1. As expected, we observe higher total visits on average.

Our data confirms that the FDA warning reduced the number of search ads by pharmaceutical firms. As displayed in Figure 2, from March to April 2009, the fraction of pharmaceutical websites in our sample that purchased a search ad dropped from approximately 50 to 10%.[9] For the other websites in our data, we do not observe a corresponding change in

[9]For websites that received clicks from fewer than three unique users and therefore were below the comScore minimum reporting standards, we assume that no paid ads were present. We find a similar pattern if we graph the number of paid clicks over this period, assuming that such advertisers receive either one or two clicks.

ad purchasing; 12 and 14% of these websites display paid ads in March and April 2009.

Though the majority of search ads was removed, some pharmaceutical companies continued displaying their ads, but with dramatically changed text. For example, Eli Lilly tried to circumvent the fair balance requirements by removing any mention of treatment in its ads. An ad for the drug Cialis might provide a link to the official website and text that merely states, "Official Site. Free Trial Voucher."[10] Therefore, the prohibition of selectively informative ads by the FDA captures both the removal of actual ads by pharmaceutical companies and the removal of informative content within ads by pharmaceutical companies. We later use this variation in compliance to compare outcomes from the policy shift in Table 6.

We also check that the dramatic shift in pharmaceutical advertising behavior did not represent changing seasonality in user behavior. Figure 2 shows the proportion of paid ads for same months in the year 2008. In this previous year within the same time frame, pharmaceutical companies only slightly decreased their paid search advertising; paid search advertising for pharmaceutical sites remained relatively the same, and there was no large and discontinuous drop between March and April as in the following year 2009.

4 Estimation and Results

We begin with graphical evidence to illustrate the effects of the policy. Figure 3 presents the total monthly clicks from searches using phrases associated with medical conditions and symptoms. The figure graphs clicks across different website types in the four months spanning the shift in enforcement policy in 2009. April and May are the months after the FDA started its new enforcement regime. An immediately and large shift downwards in the number of visits to pharmaceutical websites is apparent.

Of course, a concern is that these shifts could simply reflect seasonality. Therefore, Figure

[10] "Drug Makers to Press for Guidance on Web Marketing," Wall Street Journal, Emily Steel, November 12, 2009.

3 also presents click behavior in 2008 when no such shift in policy enforcement occurred. As expected, little change in behavior occurs across the different website categories in 2008.

Initially, we examine searches of medical conditions and symptoms in our data. We investigate how each website's share of clicks changed in response to the FDA enforcement. Note that we examine the proportion of clicks because this relative measure is not sensitive to the level or absolute number of searches. For every search term j on search engine k in month t, we compute the proportion of clicks received by website i as the number of clicks received by website i divided by the total number of clicks received by all websites for search term j on search engine k in month t.

We use the following specification to estimate how the FDA prohibition on selectively informative advertising affected consumer searches. We run the regression for the proportion of clicks:

$$\begin{aligned} Propclicks_{ijkt} &= \beta_1 Pharma_i \times PostFDA_t \\ &+ \beta_2 Nonregulated_i \times PostFDA_t \\ &+ \beta_3 Nonprofit_i \times PostFDA_t \\ &+ \beta_4 UGC_i \times PostFDA_t \\ &+ \beta_5 Commercial_i \times PostFDA_t \\ &+ \gamma_i + \alpha_j + \delta_k + \omega_t + \epsilon_{ijkt} \end{aligned} \quad (1)$$

where $Pharma$ is an indicator variable equal to 1 if the website is owned by one of the targeted pharmaceutical companies. $NonRegulated$ is an indicator variable equal to 1 if the website directs consumers to products that are not regulated by the FDA; UGC is an indicator variable equal to 1 if the website is composed of user-generated content; $Nonprofit$ is an indicator variable equal to 1 if the website is a non-profit site with an address that contains a suffix of .ORG, .EDU, or .GOV; $Commercial$ is an indicator equal to 1 if the

website is a regular commercial website. The variable $PostFDA$ is an indicator variable equal to 1 if the month occurs after March 2009, when the FDA issued the letters. Since $PostFDA$ is collinear with the month fixed effects, it drops out of the main specification. The controls γ, α, δ, and ω are website, search engine, search term and month fixed effects. The outside option or omitted website category consists of terminated search. Therefore the interaction terms should be interpreted relative to the baseline of the initial search being terminated, and a different search performed subsequently.

Table 3 presents the results.[11] The results examine overall click behavior and do not distinguish between clicks that originate from advertised or non-advertised sources. The first column includes website, keyword, and month fixed effects. The second column also adds search engine fixed effects. Note that the estimated coefficients are very similar and the same given rounding by decimal place.

Table 3 illustrates that the proportion of clicks to sites owned by pharmaceutical companies declined as a result of the change, and that clicks were diverted in general to multiple other types of sites including non-regulated sites, non-profit sites, and user-generated sites. This suggests that alternative categories of websites benefited, perhaps even mechanically, from the absence of pharmaceutical ads, since consumers had one fewer potential navigation link available. In the absence of pharmaceutical ads, people's response to the search results may shift due to changes in the composition of the information set.

Table 4 reports the changes in paid clicks (when users navigate to the website through an advertised link or search ad within the sponsored search results) and in non-paid clicks (when users navigate to the website through the non-advertised links on the main search results). We run a regression similar to Equation (1) and include additional interaction terms with $Paid$ where $Paid$ is a dummy variable equal to 1 for clicks through a paid link. The

[11] These results use ordinary least squares. We also estimated this specification using an aggregate logit specification which fully accounted for the functional form of the dependent variable, and we obtained similar results.

first column includes website, keyword, and month fixed effects. The second column also add search engine fixed effects. Note that the estimated coefficients are very similar and the same given rounding by decimal place.

The positive coefficients on the interaction terms for $PostFDA \times Non-RegulatedWebsite$, $PostFDA \times Non-ProfitWebsite$, $PostFDA \times UGCWebsite$, and $PostFDA \times CommercialWebsite$ indicate that all non-pharmaceutical categories of websites enjoyed a larger proportion of organic clicks after the change in FDA enforcement. The negative coefficient on $PostFDA \times Pharma - OwnedSite \times Paid$ suggests that pharmaceutical websites experienced a decline in the proportion of paid clicks as a result of the change in FDA enforcement.

Table 3 suggests that the policy negatively affected pharmaceutical ads and that the traffic was diverted to other categories of websites. However, one weakness with the specification in Table 3 is that it focuses on how the change in policy affected the distribution of clicks of an affected search. Specifically, Table 3 focuses on the proportion of clicks from a single search, which does not provide insight into whether the total volume of clicks changed. To understand this, we must identify a placebo group which should, absent the intervention, provide a good guideline as to the time trend we expect for the affected searches. As discussed above, we use the set of searches for medical devices to provide a baseline of activity in each month for health-related searches and users' likelihood of navigating to different categories of websites. Searches for medical devices were not affected by the shift in FDA enforcement because they were not regulated by the FDA.[12]

Figure 4 graphs the proportion of clicks in the four-month period in 2009 for website searches that involved a medical device. Reassuringly clicks to alternative categories of websites (i.e., non-profit, non-regulated, commercial, and user-contributed) do not rise in

[12]Note we observe that keyword searches on devices lead to clicks on all the different categories of websites with the exception of pharmaceutical websites. Thus this is a placebo check for non-regulated websites. We show later a placebo check for pharmaceutical websites using complying vs. non-complying pharmaceutical websites in Table 6.

the period after the FDA enforcement letters. This suggests that our results on navigation shifting from pharmaceutical websites to other alternative categories is not likely driven by seasonal differences in medical searches. Table 5 runs a regression similar to Table 4 for medical device keywords. The results confirm that we do not observe changes in the alternative categories.

4.1 Robustness Checks

We also perform numerous robustness checks in Table 6. The majority of these specifications check that our decision to exclude or include certain observations does not drive our results.

Our results remain consistent throughout these alternative specifications. Columns (1) and (2) of Table 6 shows robustness to the exclusion of visits to either the most visited or least visited 5% of websites. This is reassuring evidence that the tail of the distribution is not driving our results.[13] Columns (3) and (4) of Table 6 provide some reassuring evidence that the change we observe for pharmaceutical websites was indeed driven by the policy. We distinguish between pharmaceutical sites who completely complied with the FDA warning by removing their ads and those who only partially complied and still had a few ads after the change. As expected, the effect of the shift in FDA enforcement was greater and statistically significant for those websites that completely complied with the policy by removing all ads; the enforcement had no statistically significant effect for websites that did not comply with the policy by removing all ads. Column (5) performs a robustness check where we do not distinguish between the different search engines at the observation level. In other words, an observation is a keyword-website combination rather than a combination by keyword, search engine, and website.

One concern is that a simultaneous change occurred in offline advertising spending by pharmaceutical companies. Figure 5 presents data on offline advertising spending by phar-

[13]Earlier versions of this paper also showed similar analysis with visit time, suggesting that our results are not an artifact of changing attention spans or visits to a certain set of websites.

maceutical companies for TV, radio, and magazines from Kantar Media. Though a few peaks and troughs exist, perhaps due to industry cycles, none of the spending appears to peak or trough unusually in the period of April 2009, which could give rise to alternative explanations for our results.

Another possibility is that spending on other types of digital advertising shifted. We are unable to analyze this because Kantar did not break down its data by display advertising and paid search advertising. However, in practice, two reasons challenge the importance of display advertising during our period of study. First, display advertising was a small part of the marketing mix spend in the years that we study. In 2008, display advertising comprised of 2.4% of all advertising spending (Campbell, 2009). Further, it is not clear whether display advertising is part of the treated group of ads or the untreated group of ads. On May 12, 2009, the FTC issued a warning letter to Johnson & Johnson for a Webcast video promoting Ultram PR. This is not a drug that is in our data, but advertisers could possibly have interpreted the restrictions as applying to display advertising as well, making any interpretation of changes in spending on display advertising murky for our purposes.

A natural question is how searches themselves varied over this time period. To investigate this we gather data from Google Trends on weekly search activity for the search terms. We then analyze how the index of search activity changed for each of the terms by running a regression of the logarithm of the index on the period after the FDA announcement. We find no evidence of any changes in how often search terms were used. In the Appendix, Table A-4 reports the results.

Alternatively, we examine the possibility of search terms varying over our period of study by examining total clicks to the average pharmaceutical website in our data. We collect data from comScore on overall traffic to pharmaceutical websites. The interpretation of our results would be misplaced, if, for example, the pharmaceutical companies responded to the FDA clarification by changing their advertising and online strategies to attract website visits by

other means after the change in FDA enforcement. However, as shown by Figure 6, total visits to pharmaceutical websites had a sizeable and persistent decrease.

Another concern is that the change in FDA enforcement policy may have led to an increase in other sources of traffic for pharmaceutical websites as they expanded their digital marketing efforts beyond search engines. To explore this, we collect data on incoming traffic to pharmaceutical websites from comScore. Figure 7 illustrates two findings. First, search traffic is the dominant source of incoming traffic for the pharmaceutical websites we study. Second, no clear pattern exists of an increase in traffic from non-search sources after the change in FDA enforcement.

Figure 8 investigates whether the variety of distinct search terms that consumers used to navigate to pharmaceutical websites changed with the FDA enforcement. We collect data from comScore on search terms used to navigate to pharmaceutical websites. After the FDA enforcement notice, the variety of search terms (as measured by the number of unique or distinct search terms) that led to pharmaceutical websites declined. This reflects the fact that lack of advertising on medical conditions reduced the ability of pharmaceutical sites to attract traffic from searchers who perhaps did not have the pharmaceutical company website in mind when they searched.

4.2 The Role of Paid and Non-Paid Links

To further explore when advertising restrictions matter and when they *don't* matter, we contrast the results in the previous section of searches on conditions or symptoms with searches on a specific brand. Table 7 presents results for brand searches for a specification similar to Table 3. The first column includes website, keyword, and month fixed effects. The second column also add search engine fixed effects.[14]

Table 7 suggests that the FDA enforcement action had less of an effect for consumers who were already aware of the pharmaceutical brand's existence. Though a reduction in visits

[14]Note that the estimated coefficients are very similar and the same given rounding by decimal place.

occurred from paid clicks (as seen by the negative coefficient on $PostFDA \times Pharma - OwnedWebsite \times Paid$), this is attenuated by an increase in visits attributable to organic clicks (as seen in the positive coefficient on $PostFDA \times Pharma - OwnedWebsite$).[15] In other words, the organic channel can act as a substitute for the paid channel under searches on brands as opposed to searches on conditions and symptoms in Table 3. This echoes the findings of Blake et al. (2015). One potential explanation is that when users search on brand names, they are conducting a "navigational search" where they already know the website property they want to visit (Bechtold and Tucker, 2014). As a consequence, the presence or absence of advertising does not change their ultimate behavior. By contrast, those who search on conditions or systems are conducting a "non-navigational" search and consequently are more likely to be affected by the presence or absence of a pharmaceutical website link. These users are exploring and therefore less likely to have a destination in mind when they start searching.

To summarize, a comparison of searches for brands and for medical conditions and symptoms helps illuminate the underlying reason for our results. The comparison between the estimates in Table 3 and Table 7 suggests that the removal of selectively informative advertising is more likely to affect traffic to a pharmaceutical website when the searcher is using a search term linked with a condition or symptom. However, for consumers already aware of and searching on a pharmaceutical brand, selectively informative advertising does not significantly affect total clicks to the website. One explanation is that the position of the organic link for the pharmaceutical website is lower for searches that do not use the brand name; as a consequence, it is not possible for the paid and non-paid channel to act as substitutes for these non-branded searches. In general, given the larger volume of searches on medical conditions compared to brand keywords, the overall effect of the FDA restrictions on advertising appears to have diverted online traffic to websites that promote health sectors

[15]Note that the overall effect, which combines paid and non-paid clicks, is still negative.

not regulated by the FDA.

5 Implications and Conclusion

5.1 Implications

To understand the implications of our findings that regulating selectively provided information may lead consumers to seek non-regulated websites, it is useful to calibrate whether the non-regulated websites provided similar, better, or worse information than the regulated websites. To assess this, we implemented a survey where we asked survey participants how they viewed the reliability of a website.[16] For each non-regulated website, we asked participants to respond on a Likert scale of 1 (entirely disagree) to 7 (entirely agree) regarding several statements of whether the website feels reliable, trustworthy, could damage my well-being, or could improve my health.

Figure 9 presents the ratings for non-regulated website in a variety of dimensions. The figure indicates that participants did not feel strongly that the unregulated websites were particularly reliable, helpful, or able to improve their well-being. At the same time, participants did not view the websites as a serious threat to their health. The overall takeaway is that participants did not view unregulated websites as particularly helpful or impactful to improving their health.

5.2 Conclusion

An obvious critique of advertising is that ads provide one-sided information and that such one-sidedness may be harmful if consumers are relatively ill-informed about the risks or quality of a product, as often is in the case of the health and financial sectors. In response to concerns that companies may provide selective information in their ads, regulators have imposed restrictions on the type and amount of information disclosed within advertisements. By examining a recent change in FDA policy enforcement in March 2009, we study how

[16] We used Amazon Mechanical Turk to perform this survey.

prohibiting ads with selectively-chosen information affects consumer behavior. Our paper asks whether consumers respond by seeking information from other alternative sources and whether these sources provide more reliable or balanced information.

We find that restricting pharmaceutical advertising does not necessarily lead consumers to seek more balanced sources of information. The major beneficiaries of the restrictions appear to be channels not regulated by the FDA, such as Canadian pharmacies and purveyors of alternative homeopathic remedies. We also find some evidence that a sizable number of consumers may increasingly rely on non-verified information from the public in the form of user-generated content. We emphasize that this is not necessarily harmful, as some papers have shown the usefulness of user-generated content sites for consumers seeking health information (McNab, 2009; Moorhead et al., 2013). However, others have also documented that user-generated sites can be used for misinformation (Chiou and Tucker, 2018). Recent research looking at the Zika pandemic found on balance that there was more misleading rather than helpful information (Sharma et al., 2017) on such websites.

Our results have direct public policy implications for the regulation of advertising. They suggest that imposing regulation on advertising by "unreliable" sources of information may not necessarily improve consumers' information set, since users may seek more unverified information through non-advertised channels. Furthermore, our results suggest that expanding restrictions to other forms of advertising media may likely to lead to similar problems where users re-direct their attention to less official sources of information. For example, the FDA has more recently turned its scrutiny to advertising on social networking sites.[17]

Of course, limitations exist to our findings. First, we study short-run effects. In the long run, consumers may become more experienced at identifying better sources of information. Second, we do not study how the platform provider (or search engine) may respond to

[17]On August 2010, the FDA issued a warning letter to Novartis over its use of Facebook's "share" button, citing that the resulting text did not disclose the side-effects of the drug (Heine, 2010).

regulatory changes and how these responses may change our findings. We have been told that eventually Google was able to format its ads in such a way that satisfied the FDA, and ads were consequently restored. In the long-run, the incentives of a platform may mitigate the effects of regulation. Third, the fact that we have aggregate data rather than individual-level data means we cannot track how subsequent actions (beyond the first website visited) of each individual evolved in response to the change in FDA enforcement. Fourth, a new literature (Lewis and Reiley, 2014; Lewis and Rao, 2016) emphasizes the difficulty of measuring the small effects of advertising on actual sales. It thus remains a question the extent to which changes in advertising ultimately affected customer behavior, especially given the relatively small proportion of clicks directed to the pharmaceutical company websites. Finally, it is possible that net benefits might occur if people assume that advertising provides regulated information whereas unadvertised sources do not. Notwithstanding these limitations, we believe that our results shed light on the some potential pitfalls and complexities associated with the regulation of online advertising.

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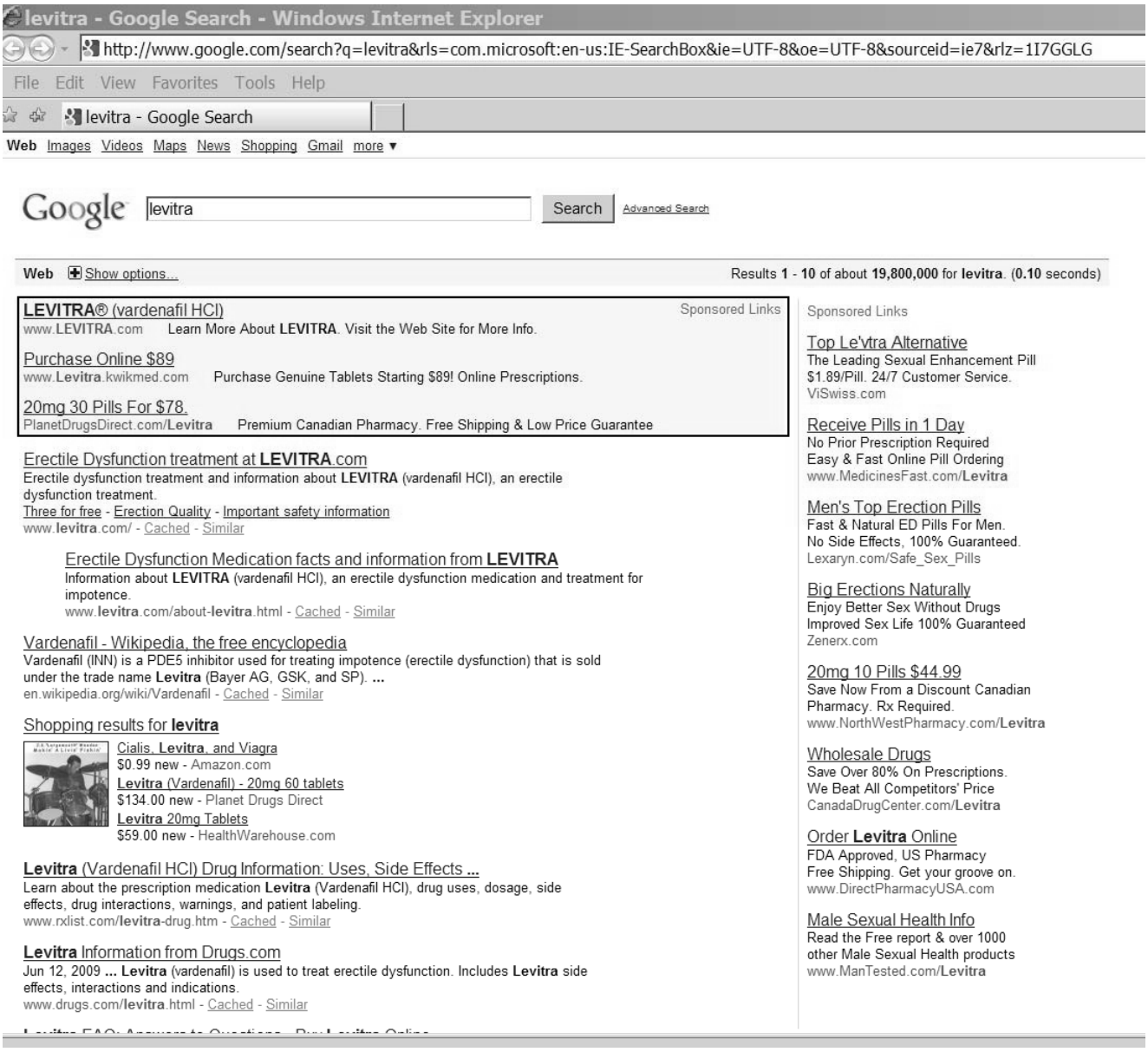
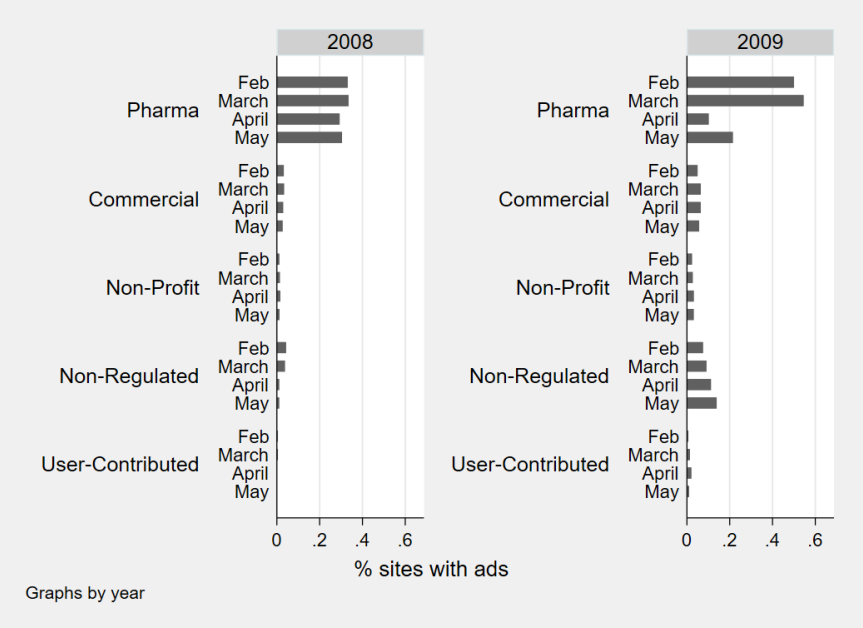
Figure 1: Typical search engine query results



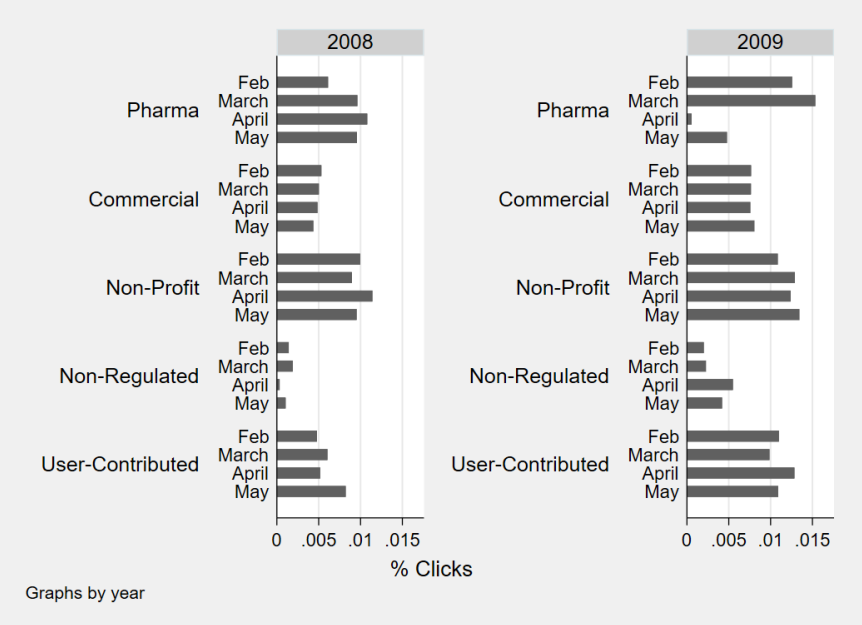
Notes: This is the search results page from a keyword search on the drug "Levitra" in Google. The paid links appear in the sponsored results sections at the top and on the right side of the page. The non-paid links appear separately. (We added a box to indicate the shaded portion of the results page.)

Figure 2: By Website Type: How the fraction of search ads changed



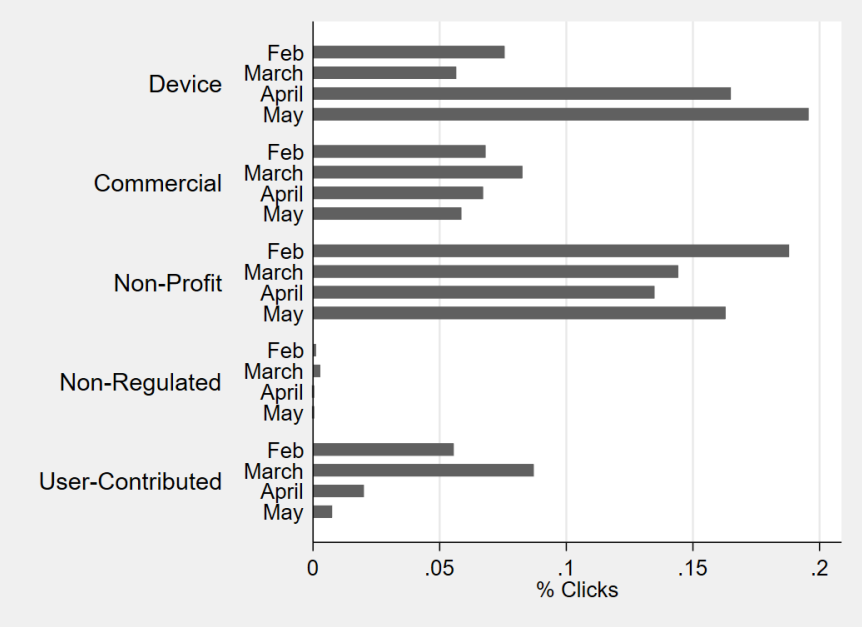
Notes: This figure compares the 4-month period in 2009 when there was a change in FDA enforcement policy with the same 4-month period in 2008 when there was not. It shows the number of search ads by different types of websites. These search ads were associated with keyword searches containing the brand name or associated medical condition and symptoms of the pharmaceutical products targeted by the FDA.

Figure 3: By Website Type: How the proportion of clicks changed for medical conditions and symptoms.



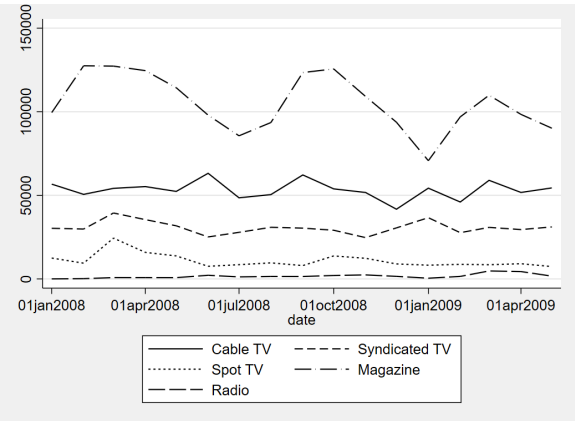
Notes: This figure compares the 4-month period in 2009 when there was a change in FDA enforcement policy with the same 4-month period in 2008 when there was not. The clicks are for keyword searches on medical conditions and symptoms.

Figure 4: By Website Type: How the proportion of clicks changed for medical devices.



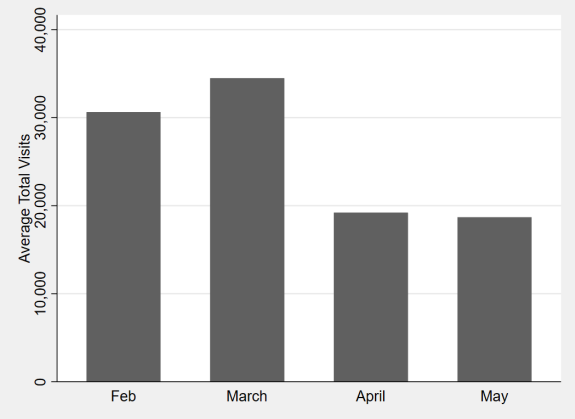
Notes: This figure compares the 4-month period in 2009 for keyword searches on medical devices, which was not covered by the FDA regulation.

Figure 5: No systematic change in offline spending on advertising occurred during change in FDA enforcement policy



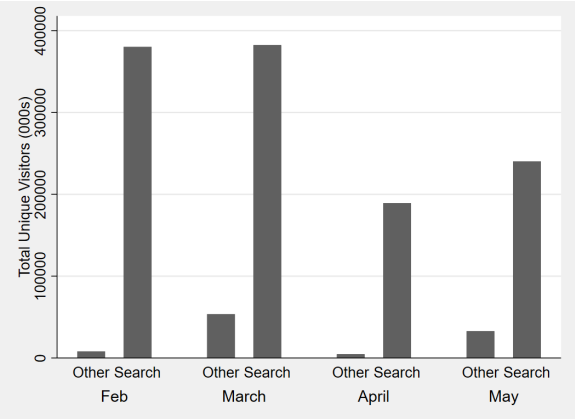
Notes: This figure shows data on pharmaceutical advertising in a variety of offline channels over the period studied in this paper.

Figure 6: How the Number of Visits to Pharmaceutical Websites Changed in 2009.



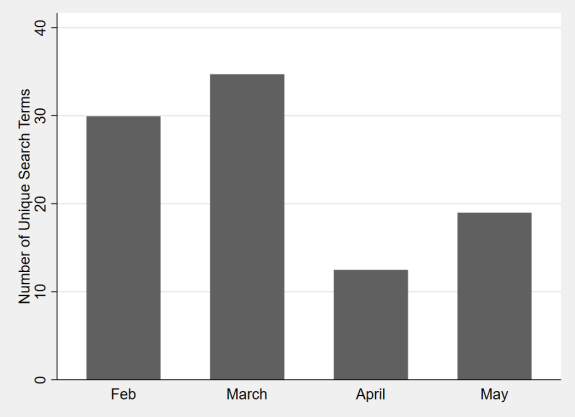
Notes: This figure shows the average of total traffic to pharmaceutical websites in our sample. This covers the time period two months before and after the FDA policy change in April.

Figure 7: How Sources of Incoming Traffic to Pharmaceutical Websites Changed in 2009.



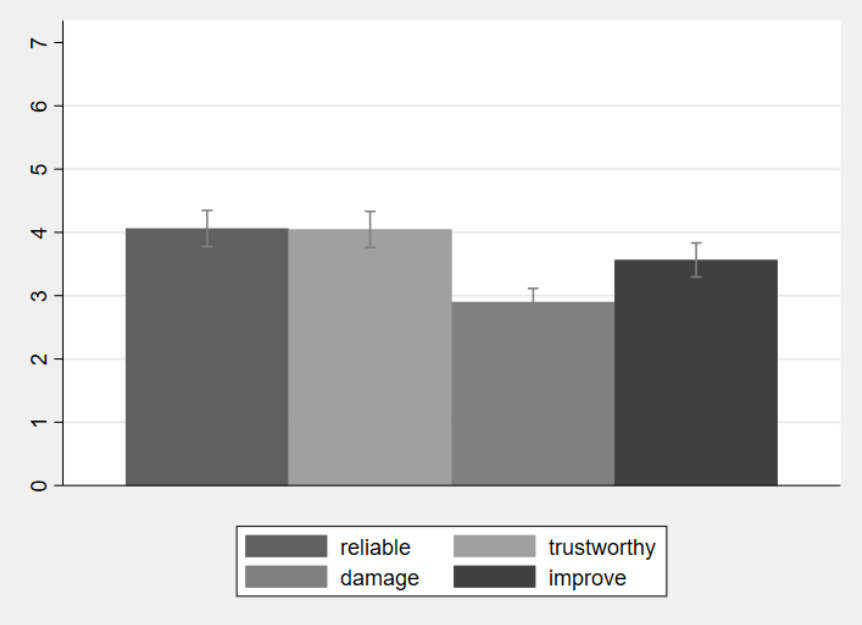
Notes: This figure graphs the total number of unique visitors (in thousands) incoming to pharmaceutical websites from search traffic vs. other traffic. This covers the time period two months before and after the FDA policy change in April.

Figure 8: How the Variety of Search Terms to Pharmaceutical Websites Changed in 2009.



Notes: This figure graphs the total number of unique or distinct search terms that led visits to pharmaceutical websites. This covers the time period two months before and after the FDA policy change in April.

Figure 9: Average ratings of quality for non-regulated websites.



Notes: Participants' ratings of quality of non-regulated websites on a scale of 1 (entirely disagree) to 7 (entirely agree). The figure reports the average ratings with confidence intervals.

Table 1: Summary statistics

	Mean	Std Dev	Min	Max	Observations
Total Clicks	1541.6	6541.7	2	305233	52064
Non-Paid Clicks	1421.5	6398.6	2	299024	52064
Paid Clicks	120.3	1071.4	2	53543	52064
PostFDA	0.50	0.50	0	1	52064
Pharma Website	0.012	0.11	0	1	52064
Non-Regulated Website	0.011	0.10	0	1	52064
UGC Website	0.021	0.14	0	1	52064
Non-Commercial Website	0.23	0.42	0	1	52064
Commercial Website	0.68	0.47	0	1	52064
Terminate	0.031	0.17	0	1	52064
Observations	52064				

Notes: Each observation represents a website and keyword combination from a given search engine during a particular month. The data includes searches on the three main search engines (Google, Yahoo!, and Live) and spans the periods from February 2009 to June 2009. The variable Post-FDA indicates the period after the FDA ruling. The types of websites in our sample include pharmaceutical, non-regulated, UGC, non-profit, and commercial. The data includes information on click behavior from keyword searches that contained the associated medical conditions and symptoms for the pharmaceutical products targeted by the FDA.

Table 2: Summary statistics: Site Level

	Mean	Std Dev	Min	Max	Observations
Total Clicks	6106.3	54736.9	2	2304408	13144
Non-Paid Clicks	5630.5	54162.8	2	2292944	13144
Paid Clicks	476.5	4430.7	2	227421	13144
Pharma Website	0.013	0.11	0	1	13144
Non-Regulated Website	0.015	0.12	0	1	13144
UGC Website	0.0070	0.083	0	1	13144
Non-Commercial Website	0.23	0.42	0	1	13144
Commercial Website	0.73	0.44	0	1	13144
Terminate	0.0049	0.070	0	1	13144
Observations	13144				

Notes: Each observation represents a single website from February 2009 to June 2009. The variable Post-FDA indicates the period after the FDA ruling. The types of websites in our sample include pharmaceutical, non-regulated, UGC, non-profit, and commercial. The data includes information on click behavior from keyword searches that contained the brand name or associated medical conditions and symptoms for the pharmaceutical products targeted by the FDA.

Table 3: Restrictions on selectively informative advertising change search behavior

	(1)	(2)
PostFDA × Pharma-Owned Website	-0.00708*	-0.00708*
	(0.00401)	(0.00401)
PostFDA × Non-Regulated Website	0.00531**	0.00531**
	(0.00238)	(0.00238)
PostFDA × Non-Profit Website	0.00370*	0.00370*
	(0.00191)	(0.00191)
PostFDA × UGC Website	0.00410**	0.00410**
	(0.00206)	(0.00206)
PostFDA × Commercial Website	0.00280	0.00280
	(0.00172)	(0.00172)
Search Engine Fixed Effects	No	Yes
Website Fixed Effects	Yes	Yes
Keyword Fixed Effects	Yes	Yes
Month Fixed Effects	Yes	Yes
Observations	52064	52064
R-Squared	0.191	0.209

Notes: Robust standard errors are clustered at the website level. $^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$. The dependent variable is the proportion of clicks to that type of website for keyword searches on medical conditions or symptoms. The regressions estimate click behavior before and after the FDA change in enforcement. Pharmaceutical websites are sites maintained by the pharmaceutical companies targeted by the FDA. Non-regulated websites includes sites that promote medical solutions either prohibited or not subject to regulation by the FDA, such as homeopathic remedies. UGC websites are sites that contain information posted by community members. Non-profit websites include governmental or non-profit sites. Commercial websites span other commercial websites. The omitted or baseline category is instances where the user terminates the search.

Table 4: Restrictions on selectively informative advertising change search behavior for paid vs. non-paid clicks

	(1)	(2)
PostFDA × Pharma-Owned Website × Paid	-0.0743***	-0.0743***
	(0.0141)	(0.0141)
PostFDA × Non-Regulated Website × Paid	-0.00105	-0.00105
	(0.00776)	(0.00776)
PostFDA × Non-Profit Website × Paid	-0.00794*	-0.00794*
	(0.00463)	(0.00463)
PostFDA × UGC Website × Paid	-0.00750	-0.00750
	(0.00481)	(0.00481)
PostFDA × Commercial Website × Paid	-0.00801*	-0.00801*
	(0.00457)	(0.00457)
PostFDA × Pharma-Owned Website	0.00248	0.00248
	(0.00196)	(0.00196)
PostFDA × Non-Regulated Website	0.00507***	0.00507***
	(0.00172)	(0.00172)
PostFDA × Non-Profit Website	0.00407***	0.00407***
	(0.00151)	(0.00151)
PostFDA × UGC Website	0.00450***	0.00450***
	(0.00142)	(0.00142)
PostFDA × Commercial Website	0.00346***	0.00346***
	(0.00131)	(0.00131)
Search Engine Fixed Effects	No	Yes
Website Fixed Effects	Yes	Yes
Keyword Fixed Effects	Yes	Yes
Month Fixed Effects	Yes	Yes
Observations	104128	104128
R-Squared	0.164	0.176

Notes: Robust standard errors are clustered at the website level. $^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$. The dependent variable is the proportion of clicks to that type of website for keyword searches on medical conditions or symptoms. The regressions estimate click behavior before and after the FDA change in enforcement. Pharmaceutical websites are sites maintained by the pharmaceutical companies targeted by the FDA. Non-regulated websites includes sites that promote medical solutions either prohibited or not subject to regulation by the FDA, such as homeopathic remedies. UGC websites are sites that contain information posted by community members. Non-profit websites include governmental or non-profit sites. Commercial websites span other commercial websites. The omitted or baseline category is instances where the user terminates the search.

Table 5: Placebo Check: Medical Devices

	(1)	(2)
PostFDA × Device-Owned Website × Paid		-0.0561
		(0.0869)
PostFDA × Non-Regulated Website × Paid		-0.0154
		(0.0165)
PostFDA × Non-Profit Website × Paid		-0.0299
		(0.0432)
PostFDA × UGC Website × Paid		-0.0145
		(0.0579)
PostFDA × Commercial Website × Paid		-0.0463
		(0.0364)
PostFDA × Device-Owned Website	0.128*	0.0813
	(0.0693)	(0.0619)
PostFDA × Non-Regulated Website	0.00915	0.0100
	(0.0118)	(0.0115)
PostFDA × Non-Profit Website	-0.00375	0.0120
	(0.0382)	(0.0373)
PostFDA × UGC Website	-0.0440	-0.0323
	(0.0300)	(0.0309)
PostFDA × Commercial Website	0.00363	0.0226
	(0.0295)	(0.0267)
Search Engine Fixed Effects	Yes	Yes
Website Fixed Effects	Yes	Yes
Keyword Fixed Effects	Yes	Yes
Month Fixed Effects	Yes	Yes
Observations	1284	2568
R-Squared	0.436	0.408

Notes: Robust standard errors are clustered at the website level. $*p < 0.1$, $**p < 0.05$, $***p < 0.01$. The dependent variable is the proportion of clicks to that type of website for keyword searches on medical devices. The regressions estimate click behavior before and after the FDA change in enforcement. Device websites are sites maintained by the device manufacturers, which are not covered by the FDA. They serve as an analogue to pharmaceutical websites in Table 3. Non-regulated websites includes sites that promote medical solutions either prohibited or not subject to regulation by the FDA, such as homeopathic remedies. UGC websites are sites that contain information posted by community members. Non-profit websites include governmental or non-profit sites. Commercial websites span other commercial websites. The omitted or baseline category is instances where the user terminates the search.

Table 6: Robustness Checks and Compliance

	Exclude Least Visited	Exclude Most Visited	Non-Complying Pharma	Complying Pharma	Collapsed Search Engines
	(1)	(2)	(3)	(4)	(5)
PostFDA × Pharma-Owned Website	-0.00713*	-0.00708*	0.00185	-0.00863**	-0.0151**
	(0.00401)	(0.00401)	(0.00809)	(0.00434)	(0.00731)
PostFDA × Non-Regulated Website	0.00539**	0.00531**	0.00531**	0.00531**	0.00640**
	(0.00241)	(0.00238)	(0.00238)	(0.00238)	(0.00279)
PostFDA × Non-Profit Website	0.00377*	0.00291*	0.00370*	0.00370*	0.00465**
	(0.00194)	(0.00177)	(0.00191)	(0.00191)	(0.00231)
PostFDA × UGC Website	0.00413**	0.00410**	0.00410**	0.00410**	0.00523**
	(0.00207)	(0.00206)	(0.00206)	(0.00206)	(0.00251)
PostFDA × Commercial Website	0.00282	0.00269	0.00280	0.00280	0.00343*
	(0.00173)	(0.00170)	(0.00172)	(0.00172)	(0.00198)
Search Engine Fixed Effects	Yes	Yes	Yes	Yes	No
Website Fixed Effects	Yes	Yes	Yes	Yes	Yes
Keyword Fixed Effects	Yes	Yes	Yes	Yes	Yes
Month Fixed Effects	Yes	Yes	Yes	Yes	Yes
Observations	49464	49684	51512	51968	40400
R-Squared	0.207	0.217	0.210	0.209	0.267

Notes: Robust standard errors are clustered at the website level. $*p < 0.1$, $**p < 0.05$, $***p < 0.01$.
Table 6 replicates the results for Table 3 and shows that it is robust to the exclusion of high traffic and low traffic sites in Columns (1) and (2). Columns (3) and (4) show how our estimates for the coefficient on $PostFDA \times Pharma$ change if we focus on pharmaceutical companies that complied and those that did not comply. As expected, the estimated coefficient on $PostFDA \times Pharma$ is small and not statistically significant for websites of pharmaceutical companies that did not comply and did not withdraw their ads. The estimated coefficient on $PostFDA \times Pharma$ is negative, large, and statistically significant for websites of pharmaceutical companies that did comply and withdraw their ads. Column (5) shows estimates if we do not distinguish between different search engines at the observation level. The dependent variable is the logarithm of total clicks. The regressions estimate click behavior before and after the FDA change in enforcement. Pharmaceutical websites are sites maintained by the pharmaceutical companies targeted by the FDA. Non-regulated websites includes sites that promote medical solutions either prohibited or not subject to regulation by the FDA, such as homeopathic remedies. UGC websites are sites that contain information posted by community members. Non-profit websites include governmental or non-profit sites. Commercial websites span other commercial websites.

Table 7: Effects are different for searches on brand name

	(1)	(2)
PostFDA × Pharma-Owned Website × Paid	-0.254***	-0.254***
	(0.0404)	(0.0404)
PostFDA × Non-Regulated Website × Paid	0.0197	0.0197
	(0.0246)	(0.0246)
PostFDA × Non-Profit Website × Paid	-0.00542	-0.00542
	(0.0118)	(0.0118)
PostFDA × UGC Website × Paid	-0.00251	-0.00251
	(0.00925)	(0.00925)
PostFDA × Commercial Website × Paid	0.00495	0.00495
	(0.00910)	(0.00910)
PostFDA × Pharma-Owned Website	0.0588**	0.0588**
	(0.0296)	(0.0296)
PostFDA × Non-Regulated Website	0.00831	0.00831
	(0.00774)	(0.00774)
PostFDA × Non-Profit Website	0.00821	0.00821
	(0.0113)	(0.0113)
PostFDA × UGC Website	0.00390	0.00390
	(0.00753)	(0.00753)
PostFDA × Commercial Website	-0.000962	-0.000962
	(0.00763)	(0.00763)
Search Engine Fixed Effects	No	Yes
Website Fixed Effects	Yes	Yes
Keyword Fixed Effects	Yes	Yes
Month Fixed Effects	Yes	Yes
Observations	7744	7744
R-Squared	0.499	0.507

Notes: Robust standard errors are clustered at the website level. $*p < 0.1$, $**p < 0.05$, $***p < 0.01$. The dependent variable is the proportion of clicks each website received for a keyword search on a pharmaceutical brand name. The regressions estimate click behavior before and after the FDA change in enforcement. Non-regulated websites includes sites that promote medical solutions either prohibited or not subject to regulation by the FDA, such as homeopathic remedies. UGC websites are sites that contain information posted by community members. Non-profit websites include governmental or non-profit sites. Commercial websites span other non-categorized websites. The baseline category is whether the user terminates the search.

A Appendix

Table A-1: Full listing of drugs, FDA approved use, product webpage, and brand keywords within data sample

Drug	FDA-approved use	Webpage	Brand Keyword
Avandamet	Avandamet is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and metformin therapy is appropriate. The PI includes important limitations to use, such that Avandamet should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, the co-administration of Avandamet and insulin is not recommended, and the use of Avandamet with nitrates is also not recommended.	AVANDAMET.COM	avandamet
Avandia	Avandia is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Avandia should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, the co-administration of Avandia and insulin is not recommended, and the use of Avandia with nitrates is also not recommended.	AVANDIA.COM	avandia
Avastin	Avastin is indicated, among other things, in combination with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.	AVASTIN.COM	avastin
Avodart	Avodart is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention (AUR), and reduce the risk of the need for BPH-related surgery.	AVODART.COM	avodart
Boniva	Boniva is indicated for the treatment and prevention of osteoporosis in postmenopausal women. Boniva increases bone mineral density (BMD) and reduces the incidence of vertebral fractures.	BONIVA.COM	boniva
Bystolic	Bystolic is indicated for the treatment of hypertension. Bystolic may be used alone or in combination with other antihypertensive agents.	BYSTOLIC.COM	bystolic
Caduet	Caduet (amlodipine and atorvastatin) is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate. The Indications and Usage section provides a detailed description of the indications for each of the drug's two active ingredients.	CADUET.COM	caduet, novasc
Campral	Campral is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. Treatment with Campral should be part of a comprehensive management program that includes psychosocial support. The efficacy of Campral in promoting abstinence has not been demonstrated in patients who have not undergone detoxification and have not achieved alcohol abstinence before initiation of Campral treatment. Additionally, the efficacy of the drug in promoting abstinence from alcohol in polysubstance abusers has not been adequately assessed.	CAMPRAL.COM	campral
Celebrex	Carefully consider the potential benefits and risks of CELEBREX and other treatment options before deciding to use CELEBREX. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals....CELEBREX is indicated [among other things]: 1) For relief of the signs and symptoms of osteoarthritis. 2) For relief of the signs and symptoms of rheumatoid arthritis in adults. 3) For relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older....	CELEBREX.COM	celebrex
Chantix	Chantix is indicated as an aid to smoking cessation treatment.	CHANTIX.COM	chantix
Cymbalta	Cymbalta is indicated, among other things, for the acute and maintenance treatment of major depressive disorder (MDD).	CYMBALTA.COM	cymbalta
Detrol	Detrol LA Capsules are once daily extended release capsules indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.	DETROLLA.COM	detrol
Diovan	Diovan is indicated, among other things, for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.	DIOVAN.COM	diovan

Continued on next page

Table A-1 – continued from previous page

Drug	FDA-approved use	Webpage	Brand Keyword
Exforge	Exforge is indicated for the treatment of hypertension. Exforge may be used in patients whose blood pressure is not adequately controlled on either [amlodipine or valsartan as] monotherapy. Exforge may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. The choice of Exforge as initial therapy for hypertension should be based on an assessment of potential benefits and risks including whether the patient is likely to tolerate the lowest dose of Exforge	EXFORGE.COM	exforge
Femara	Femara is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. Femara is indicated for the extended adjuvant treatment of early breast cancer in postmenopausal women who have received 5 years of adjuvant tamoxifen therapy. Femara is indicated for first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer. Femara is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The Indications and Usage section of the PI includes important limitations for Femara's use in the adjuvant setting, including that the effectiveness of Femara in early breast cancer is based on an analysis of disease-free survival in patients treated for a median of 24 months and followed for a median of 26 months and follow-up analyses will determine long-term outcomes for both safety and efficacy. This section also includes important limitations for Femara's use in the extended adjuvant setting, including that the effectiveness of Femara in extended adjuvant treatment of early breast cancer is based on an analysis of disease-free survival in patients treated for a median of 24 months and further data will be required to determine long-term outcome.	FEMARA.COM	femara
Flomax	Flomax is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Flomax is not indicated for the treatment of hypertension.	4FLOMAX.COM	flomax
Gemzar	Gemzar is indicated, among other things, in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell cancer.	GEMZAR.COM	gemzar
Gleevec	According to its FDA-approved PI, Gleevec is indicated for the following: - Newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase. Follow-up is limited to 5 years. - Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. - Pediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival. - Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia. - Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements. - Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown. - Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFR fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR fusion kinase negative or unknown. - Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans. - Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. - Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.	GLEEVEC.COM	

Continued on next page

Table A-1 – continued from previous page

Drug	FDA-approved use	Webpage	Brand Keyword
Herceptin	Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer: as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; with docetaxel and carboplatin; as a single agent following multi-modality anthracycline based therapy. Herceptin is also indicated in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer, or as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.	HERCEPTIN.COM	
Januvia	Januvia is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The PI includes important limitations of use, such that Januvia should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings, and that Januvia has not been studied in combination with insulin.	JANUVIA.COM	januvia
Levitra	Levitra is indicated for the treatment of erectile dysfunction.	LEVITRA.COM	levitra
Lexapro	Lexapro is indicated, among other things, for the acute and maintenance treatment of major depressive disorder (MDD) in adults and in adolescents 12 to 17 years of age.	LEXAPRO.COM	lexapro
Lyrica	Lyrica is indicated, among other things, for: . . . Management of neuropathic pain associated with diabetic peripheral neuropathy; . . . Adjunctive therapy for adult patients with partial onset seizures [and] . . . Management of fibromyalgia.	LYRICA.COM	lyrica
Mirapex	Mirapex is indicated, among other things, for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).	MIRAPEX.COM	mirapex
Mirena	Mirena is indicated for intrauterine contraception for up to 5 years. Thereafter, if continued contraception is desired, the system should be replaced. Mirena is recommended for women who have had at least one child.	MIRENA-US.COM	mirena
Namenda	Namenda is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.	NAMENDA.COM	namenda
Plavix	For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, PLAVIX has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.	PLAVIX.COM	plavix
Propecia	PROPECIA is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in MEN ONLY. Safety and efficacy were demonstrated in men between 18 to 41 years of age with mild to moderate hair loss of the vertex and anterior mid-scalp area. Efficacy in bitemporal recession has not been established. PROPECIA is not indicated in women . . . [or] children . . . "	PROPECIA.COM	propecia
Rituxan	Rituxan is indicated for the treatment of non-Hodgkin's Lymphoma (NHL) patients with: Relapsed or refractory, low-grade or follicular, CD-20-positive, B-cell, NHL as a single agent; Previously untreated follicular, CD-20-positive, B-cell NHL in combination with CVP chemotherapy; Non-progressing (including stable disease), low-grade, CD-20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy; Previously untreated diffuse large B-cell, CD20-positive, NHL in combination with CHOP or other anthracycline-based chemotherapy regimens. Rituxan in combination with methotrexate is also indicated to reduce signs and symptoms and to slow the progression of structural damage in adult patients with moderately-to-severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.	RITUXAN.COM	rituxan
Singulair	Singulair is indicated, among other things, for the relief of symptoms of allergic rhinitis (seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older, and perennial allergic rhinitis in adults and pediatric patients 6 months of age and older).	SINGULAIR.COM	singulair
Spiriva	Spiriva is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.	SPIRIVA.COM	spiriva

Continued on next page

Table A-1 – continued from previous page

Drug	FDA-approved use	Webpage	Brand Keyword
Xeloda	Xeloda is indicated, among other things, as a single agent for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred. Xeloda was non-inferior to 5-flourouracil and leucovorin (5-FU/LV) for disease-free survival and while neither Xeloda nor combination therapy increases overall survival, combination therapy has been shown to improve disease-free survival compared to 5-FU/LV. Xeloda is also indicated as first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy demonstrated a survival benefit compared to 5-FU/LV alone, however, a survival benefit over 5-FU/LV has not been demonstrated with Xeloda monotherapy.	XELODA.COM	xeloda
Yaz	YAZ is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive. YAZ is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of YAZ for PMDD when used for more than three menstrual cycles has not been evaluated. YAZ has not been evaluated for the treatment of premenstrual syndrome (PMS). YAZ is also indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy, and have achieved menarche. YAZ should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.	YAZ-US.COM	yaz

Table A-2: Medical condition keywords within data sample

Medical Condition Keywords	
aids	erection
alcoholism	fibromyalgia
allergies	hair loss
alopecia	hay fever
alzheimer	headaches
anxiety	heart attack
arthritis	hepatitis c
asthma	hiv
baldness	hypertension
birth control	incontinence
blood clots	leukemia
blood pressure	lung cancer
blood sugar	lymphoma
bph	macular degeneration
breast cancer	mdd
bronchitis	multiple sclerosis
carcinoma	neuropathy
chemotherapy	osteoporosis
cll	ovarian cancer
colon cancer	overactive bladder
contraception	pms
contraceptive	prostate cancer
cystic fibrosis	rheumatoid arthritis
dementia	runny nose
depression	sarcoma
diabetes	shingles
diabetic	smoking
diabetic neuropathy	stomach cancer
emphysema	stroke
enlarged prostate	vomiting
erectile dysfunction	

Notes: This table lists the associated medical conditions for the targeted drugs within our sample. The abbreviations are as follows: bph (benign prostatic hyperplasia), cll (chronic lymphocytic leukemia), hiv (human immunodeficiency virus), mdd (major depressive disorder), and pms (premenstrual syndrome).

A-1 Sample Warning Letter from FDA

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service Food and Drug Administration Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Margaret J. Jack Director, DRA Hoffmann-La Roche Inc., Bldg 1/2 340 Kingsland Street Nutley, NJ 07110 RE: NDA #21-455, 21-858 BONIVA (ibandronate sodium) Tablets BLA #103964 PEGASYS (peginterferon alfa-2a) for Injection NDA #20-896 XELODA (capecitabine) Tablets MACMIS ID #17318

Dear Ms. Jack:

As part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed Hoffmann-La Roche Inc.'s (Hoffmann-La Roche) sponsored links on Internet search engines (e.g., Google.com) for the following products: BONIVA (ibandronate sodium) Tablets (Boniva), PEGASYS (peginterferon alfa-2a) for Injection (Pegasys), and XELODA (capecitabine) Tablets (Xeloda). The sponsored links are misleading because they make representations and/or suggestions about the efficacy of Boniva, Pegasys, and Xeloda, but fail to communicate any risk information associated with the use of these drugs. In addition, the sponsored links for Pegasys and Xeloda inadequately communicate the drugs' indications and also fail to use the required established name. Thus, the sponsored links misbrand the drugs in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA implementing regulations. See 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 201.10(g)(1), 202.1(b)(1), (e)(3)(i), (ii) & (e)(6)(i).

Background

Boniva

According to its FDA-approved product labeling (PI), Boniva is indicated for the treatment and prevention of osteoporosis in postmenopausal women. Boniva increases bone mineral density (BMD) and reduces the incidence of vertebral fractures. Boniva is associated with a number of risks, as reflected in the Contraindications, Warnings, Precautions, and Adverse Reactions sections of its PI.

Pegasys

According to its FDA-approved PI, Pegasys is indicated, among other things, alone or in combination with Copegus (ribavirin) for the treatment of adults with chronic hepatitis C (CHC) virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Margaret J. Jack Page 2 Hoffmann-La Roche Inc. NDA #21-455, 21-858, 20-896, BLA 103964 MACMIS #17318 Pegasys is associated with a number of risks, as reflected in the Boxed Warning, Contraindications, Warnings, Precautions, and Adverse Reactions sections of its PI.

Xeloda

According to its FDA-approved PI, Xeloda is indicated, among other things, as a single agent for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor

when treatment with fluoropyrimidine therapy alone is preferred. Xeloda was non-inferior to 5-flourouracil and leucovorin (5-FU/LV) for disease-free survival and while neither Xeloda nor combination therapy increases overall survival, combination therapy has been shown to improve disease-free survival compared to 5-FU/LV. Xeloda is also indicated as first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy demonstrated a survival benefit compared to 5-FU/LV alone, however, a survival benefit over 5-FU/LV has not been demonstrated with Xeloda monotherapy Xeloda is associated with a number of risks, as reflected in the Boxed Warning, Contraindications, Warnings, Precautions, and Adverse Reactions sections of its PI. Omission of Risk Information

Promotional materials, other than reminder pieces, which include the name of the drug product but do not include indications or other representations or suggestions relative to the drug product (see 21 CFR 200.200, 201.100(f), 202.1(e)(2)(i)), are required to disclose risk and other information about the drug. Such materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The sponsored links present the following claims:

- Free Trial Offer www.Boniva.com BONIVA (ibandronate sodium). Learn About Postmenopausal Osteoporosis.
- PEGASYS Official Site www.PEGASYS.com Learn About PEGASYS & Hepatitis C Register For The E-Mail Newsletter.
- XELODA Information www.xeloda.com Learn About An Oral Chemotherapy Treatment For Colon Cancer.

These sponsored links make representations and/or suggestions about the efficacy of Boniva, Pegasys, and Xeloda, respectively, but fail to communicate any risk information. This omission of risk information is particularly concerning as two of the products, Pegasys and Xeloda, have Boxed Warnings. For promotional materials to be truthful and non-misleading, they must contain risk information in each part as necessary to qualify any claims made about the drug.

By omitting the most serious and frequently occurring risks associated with the drugs promoted in the links above, the sponsored links misleadingly suggest that Boniva, Pegasys and Xeloda are safer than has been demonstrated. We note that these sponsored links contain a link to the products' websites. However, this is insufficient to mitigate the misleading omission of risk information from these promotional materials.

Inadequate Communication of Indication

The sponsored links for Pegasys and Xeloda provide very brief statements about what the drugs are for; however, these statements are incomplete and misleading, suggesting that the drugs are useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

Specifically, the sponsored link for Pegasys misleadingly broadens the indication for Pegasys by implying that all patients with hepatitis C are candidates for Pegasys therapy (Learn About PEGASYS & Hepatitis C...), when this is not the case. Rather, Pegasys is only indicated (alone or in combination) for the treatment of

chronic hepatitis C virus infection in adults who have compensated liver disease and who have not been treated with interferon alpha previously.

Similarly, the sponsored link for Xeloda misleadingly broadens the indication for Xeloda by implying that the drug is approved to treat any type of colon cancer (Learn About An Oral Chemotherapy Treatment For Colon Cancer), when this is not the case. Rather, Xeloda's indication is limited to adjuvant treatment in patients with Duke's C colon cancer and as first-line treatment for metastatic colorectal carcinoma. Furthermore, the sponsored link fails to communicate any of the limitations to either of these indications or the drug's limited proven survival benefits.

Failure to Use Required Established Name

The sponsored links for Pegasys and Xeloda fail to present the full established name of the drugs being promoted, despite the requirement to do so. See 21 CFR 201.10(g)(1) & 202.1(b)(1).

Conclusions and Requested Action

For the reasons discussed above, the sponsored links misbrand Boniva, Pegasys and Xeloda, in violation of the Act and FDA regulations. See 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 201.10(g)(1), 202.1(b)(1), (e)(3)(i), (ii) & (e)(6)(i). DDMAC requests that Hoffmann-La Roche immediately cease the dissemination of violative promotional materials for Boniva, Pegasys and Xeloda, such as those described above.

Please submit a written response to this letter on or before April 9, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for these drugs as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such materials. Finally, we encourage you to review your promotional materials for the Margaret J. Jack Page 4 Hoffmann-La Roche Inc. NDA #21-455, 21-858, 20-896, BLA 103964 MACMIS #17318 other prescription drug products that Hoffmann-La Roche promotes in the United States and to discontinue or revise any materials with the same or similar violations, and request that your response address this issue as well.

Please direct your response to the undersigned at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 17318 in addition to the NDA numbers. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Boniva, Pegasys, and Xeloda comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

Michael Sauers Regulatory Review Officer Division of Drug Marketing, Advertising and Communications

A-2 Further Detail on Data Sources

A-2.1 ComScore

The following contains excerpts from the comScore User Guide on the methodology and data collection.

> ComScore measures the continuous online activity of more than 2 million persons worldwide. ComScore deploys passive, non-invasive measurement in its collection technologies; projects the data to the universe of persons online; and continuously strives to identify, understand, quantify, and eliminate bias to the maximum extent possible.
>
> The following are the core steps in the comScore methodology: 1. Establish the universe via enumeration; 2. Obtain respondents via online recruitment; 3. Collect data; 4. Identify the User; 5. Projection and Bias Elimination.
>
> comScore conducts a monthly enumeration survey by telephone collecting information on detailed demographics and Internet usage such as: Personal demographics (age, gender, education, etc.), Internet usage status, Connection speed, Census region, Household size, Computers in home, ISP, Operating System, AOL usage, and Work usage.
>
> Each month comScore uses data from the most recent wave of the survey and from the 11 preceding waves to estimate the proportion of households in the U.S. with at least one member using the Internet and also the average number of Internet users in these households. We then take the product of these two estimates and multiply by a Census-based estimate of the total number of households in the U.S. to get an estimate of the total number of Internet users.
>
> comScore uses an array of online recruitment techniques to acquire the members of its massive panel. These include affiliate programs and partnering with third party applications providers who meet comScore's quality standards. To recruit people members for its calibration panel, which it uses to eliminate effects of bias in the panel recruited online, comScore adheres to stringent standards for recruiting a probability sample. In all cases panelists opt-in through a registration process that includes a stringent privacy practice.
>
> During registration, panelists configure a software agent which allows comScore to "see" user activity at the machine- or screen-side resulting in a view of the user experience, as opposed to site-centric measurement. This software yields not only the URLs of web pages requested by users but also information such as search strings, products purchased and referral requests. As a result, comScore can capture just about anything exchanged using the HTTP and HTTPS protocols and others such as streaming, AOL proprietary and IM environments.
>
> All of the panelist's Internet activity is captured regardless of type of browser used. (Note: the comScore panel only includes computers running a Win32 operating system, and does not include computers using other operating systems such as McIntosh or Linux). Activity is captured regardless of whether an Internet connection is established via a commercial Internet Service Provider (ISP) or an office-hosted LAN.

Data capture and reporting are conducted in adherence to strict, industry-leading privacy protection policies. Data about user identity is stored in an encrypted, access-controlled database. Internet audience and behavior data is reported only in aggregate form.

Except for people in the calibration panel, comScore does not ask the people in its panel to identify themselves when they use the Internet. Instead, comScore infers who is at a computer at any point in time, using data that include biometric measurements (measurements of keystrokes and mouse clicks), the time of day that the computer is being used, and text strings in the data being accumulated (such as first names in forms being posted). Consequently, comScore's panelists are not constantly reminded that their Internet use is being monitored and so the monitoring is much less likely to influence their use of the Internet.

comScore calculates and applies weights to the data accumulated for panelists when aggregating the data to get the measurements it publishes. One purpose of these weights is to project measurements made across the Internet users in the Panel to the much larger number who are not. The other purpose is to eliminate the bias that published estimates would otherwise have because online recruitment yields disproportionately few or many people from some segments of Internet users (for example, too many intensive Internet users and too few Internet users from high income households). Panelists from a segment that is more poorly represented get bigger weights and those from a segment that is over-represented get smaller weights.

Targets for the distribution of these weights have two sources: the enumeration survey and a "calibration panel." The enumeration survey provides targets for the distribution of weights across categories of demographic variables, such as gender, age group and household income. The calibration panel is a panel of Internet users recruited using methods that comply with stringent standards for obtaining a probability sample. comScore's software is installed on the computers of people in the calibration panel, and the data accumulated for these panelists is used to derive targets for the distribution of weights across categories of behavioral variables, such as total minutes of Internet use.

The core metric in comScore Marketer is the distinct search query, which most accurately tracks the user intent to search. A searcher must execute a search in order for a Search to be credited to the web entity that delivers the search results (not from where the search is initiated).

The definition of a search is:

- A user interaction where the user is presented with a search result page
- The search result page allows the user with the ability to refine or change their search parameters.
- Search can be initiated from a drop down or clicking a link, as long as first two rules are satisfied

All push-traffic and non-user requested activity is filtered from comScore Marketer via comScore's Client Focus Dictionary rules and outlier processing. The following do not count as a search, and are not reported in the comScore Marketer data: BOT activity, auto search DNS error page activity, or double-counted meta-search activity.

ComScore currently reports on both organic and paid click activity observed on the following entities: AOL Prop Web Search, AOL.com Web Search, Ask reply page, Google Web Search, MSN-Windows Live Web Search/MSN

Web Search, and Yahoo! Web Search.

comScore Marketer utilizes comScore's Client Focus Dictionary with its categorized 6-level hierarchy but extends reporting to non-categorized media as well. A media domain is eligible to be reported based on visitation of at least 30 tracked machines during the time period.

A-3 Creation of Balanced Panel

One drawback of the way that comScore records its data is that it does not allow researchers to disentangle cases where a link was not presented or not seen, and cases where consumers en masse chose not to click on a website. This is a concern because in our data though all 99.992% of each website-search term combination had some instance when there was recordable activity by comScore, activity was not recorded in all months in 37.62% of cases in our data. To reassure ourselves that this was not driving our results we check that such non-observation was not unevenly spread across website type. Pharmaceutical websites recorded activity in 62.3% of months, and non-pharmaceutical websites recorded activity in 61.9% of months. A t-test suggested no statistical difference between these two means.

Table A-3: Keywords for medical devices associated with medical conditions in data sample

Medical device keywords
air mask
allergy mattress covers
blood glucose meter
breast implants
compression stockings
coronary stent
distal protection device
dust covers
dust mask
feeding tube
glucose test
heart stent
humidifier
insulin pen
insulin pump
insulin syringes
insulin test
IV lines, PICC lines, central lines
lens implant
nebulizer
oxygen mask
penile implant
penile pump
pessary
rubber bulb ear syringe
spirometer
tissue expanders

Notes: This table lists the associated medical devices for the medical conditions within our sample.

Table A-4: Google Trends

	(1) All	(2) Conditions+Symptoms	(3) Pharma	(4) Device
PostFDA	-0.0103	0.00902	-0.0152	-0.0913
	(0.0400)	(0.0435)	(0.0964)	(0.0950)
Search Term Fixed Effects	Yes	Yes	No	No
Observations	532	308	160	64
R-Squared	0.0897	0.00296	0.000158	0.0147

Notes: Robust standard errors are clustered at the website level. $^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$. The regressions estimate the logarithm of search index for search terms before and after the FDA announcement. Column (1) includes all search terms used in this study. Column (2) includes search terms for conditions and symptoms. Column (3) includes pharmaceutical brand keywords. Column (4) contain search terms for medical devices. For regressions that pool different categories of search terms (e.g., conditions and symptoms), we include fixed effects for each category.