WORKING PAPERS

N° 1459

July 2023

"Strategic Submissions: A Cross-Country Analysis of Supplemental Drug Approvals"

Pierre Dubois, Elissa Philip Gentry, Tuba Tuncel

Toulouse School of Economics

Strategic Submissions: A Cross-Country Analysis of Supplemental Drug Approvals

Pierre Dubois Elissa Philip Gentry Tuba Tunçel*

July 31, 2023

Abstract

Off-label use regulation has the potential to change pharmaceutical firms' behavior and—consequently—affect patient welfare. We investigate the impact of two changes in off-label regulation on pharmaceutical firms' behavior in seeking formal marketing approval for supplementary uses. In 2012, a US court decision protected truthful off-label promotion, providing pharmaceutical companies more leeway to promote off-label uses of their drug. Similarly, in 2011, France passed a new system for monitoring off-label uses in anticipation of formal approval. Using a unique data set of pharmaceutical firms' research and development projects, we exploit these regulatory changes to understand how firms react to government policies. Results demonstrate that firms responded to the US policy providing lower incentives to submit supplemental uses for formal approval. The results do not evince any reaction to France's stringent—but poorly enforced—regulation. These results have implications not only for innovation policy but for the creation of high-quality data for certain indications.

*Dubois: Toulouse School of Economics, pierre.dubois@tse-fr.eu; Gentry: Florida State University College of Law, egentry@law.fsu.edu; Tunçel: Florida State University, ttuncel@fsu.edu. The authors gratefully acknowledge funding from the Agence Nationale de la Recherche under grant ANR-17-EURE-0010 (Investissements d'Avenir program), and funding from the TSE-P Health Center whose lists of sponsors can be found at https://www.tse-fr.eu/health.

Keywords: Pharmaceutical Firm Behavior, Prescription Drugs, Drug Efficacy, Off-Label Drugs.

JEL Codes: I10, D22, L20, I18

1 Introduction

All developed countries require pharmaceutical companies to receive approval for at least one drug use before the drug is marketed. The extent of this approval process varies by country, but the requirement to complete a market authorization process is uniform. Regulatory agencies approve drugs only for the specific indications requested by pharmaceutical companies, not for general use.

A company's decision to submit a drug use for formal approval considers common factors: the relevant costs of approval (e.g., cost of scientific studies, administrative procedure, and government incentives to innovate) and benefits of approval (e.g., expected market size and price). The types of costs and benefits, however, differ based on whether the approval is the first for the drug (an "original" approval) or an additional approval (a "supplemental" approval).

For an original use, formal approval grants access to the market for the drug substance, as unlicensed use of a drug is uniformly illegal. Once a drug has been approved for one indication, however, its prescription and consumption for a disease for which it was *not* approved is considered legal by most countries, a phenomenon known as "off-label" use.[1] Physicians are generally free to prescribe drugs for off-label uses, not just approved uses. The continued access to the market constitutes a significant difference for supplemental uses.

While off-label prescription is generally legal, most countries have placed restrictions on the ability of pharmaceutical companies to advertise off-label uses to physicians through a

[1]Off-label prescription can refer to the prescription of a drug for a different population, in a different dose, or for a different disease (hereinafter "indication") than that for which it was formally approved. This paper will concentrate on the prescription of drugs for different indications.

process called "detailing" or "promotion". While promotion is legal for on-label uses in most countries, most countries rely on restricting pharmaceutical promotion of off-label uses to providers,[2] under the rationale that pharmaceutical companies have too great an incentive to falsely represent off-label uses of their drug for economic purposes.[3]

Countries' willingness to allow off-label prescription reflects the tension between two interests: 1) access to innovative treatments and 2) the creation of new scientific information. Given the expense and delay associated with formal approval,[4] waiting for potential treatments to receive approval can unnecessarily limit physician practice of medicine: physicians seeking alternative cures for patients for whom approved treatments have failed—or for whom approved treatments are not well-tolerated—may demand medical alternatives, which off-label uses supply. Indeed, off-label use is very common. The most comprehensive study on off-label prescriptions, using nationally representative data, found that among the 160 most commonly prescribed drugs in the U.S., off-label prescriptions account for approximately 21% of overall use (Radley et al., 2006). It reports that off-label uses comprise 46% of cardiac therapies, 46% of anticonvulsants, 42% of antiasthmatics, 34% of allergy therapies, and 31% of psychiatric therapies. This high prevalence reflects the potential benefits associated with allowing physicians greater freedom in their prescription decisions. Tunçel (2023) shows that among French general practitioners 21% of drugs prescribed for depression treatment are off-label drugs and that, in terms of health outcomes, such uses are not worse than approved alternatives.

On the other hand, rigorous scientific study is often only undertaken in order to receive regulatory approval. Not all scientific data are created equal: robust evidence of efficacy and safety is best created by double-blind, randomized controlled study. Moreover, large-scale studies have better chances of identifying rarer safety risks. Such expensive studies are most

[2]This paper will not focus on direct-to-consumer advertising, but it is worth noting that most countries prohibit direct-to-consumer advertising in general, with the United States being a notable exception.

[3]Countries also often restrict reimbursement of off-label uses.

[4]Notably, the US government has attempted to create incentives to do so by subsidizing applications for drugs targeted to rare diseases Yin (2009).

likely to be undertaken by pharmaceutical companies in pursuit of formal approval. Given that pharmaceutical companies are not required to present results to justify off-label uses of their drug, rigorous evidence regarding the safety and efficacy for off-label uses is scarce. Radley et al. (2006) report that only 27% of off-label uses were supported by strong scientific evidence. In other cases, physicians rely on inferences from formal approval of a drug in a similar class or reports of documented side effects of the drug. Physicians may also rely on small-scale studies or anecdotes from colleagues to attempt a novel treatment. This is neither the most robust way to support a treatment decision nor a proper incentive for the creation of better public scientific information about a use.

Against this backdrop, this paper focuses on two distinct changes in off-label drug use policy. The United States recently relaxed its restrictions on off-label promotion based on the theory that such promotion is protected by the First Amendment. After a circuit ruling extending this protection to off-label promotion, increasing the relative benefits associated with keeping a use off-label, we expect that firms are subsequently less likely to apply for formal approval for supplemental uses. The second regulatory change occured in France. With a system of registration and tracking off-label uses, France attempted to create transparency for off-label uses by creating an observation window of up to 3 years before approval. While this regulation had the potential to restrict off-label prescriptions, lax enforcement can undermine this change in expectations–even potentially providing an incentive to keep uses off-label.

Using a unique data set listing the research and development projects for pharmaceutical firms, this paper exploits these regulatory changes in the United States and France to understand the effect of government incentives on firms' decisions to submit uses for formal approval. We find that the expectation of more relaxed off-label promotion regulations led to a lower hazard of formal supplemental approval in the US. These results are robust to a variety of specifications and to within and across country comparisons. We do not find evidence of a change in hazard of approval in France after the change in regulation.

This paper adds to the prior literature on incentives to innovate. It is well-documented that firms strategically respond to government incentives to bring products to market. Cockburn et al. (2016) analyze this issue in the context of drug launches across countries. Focusing on the effects of price regulation of pharmaceuticals and corresponding patent protection, Cockburn et al. (2016) find that the former delays launch while the latter accelerates it. Similarly, Yin (2009) considers government in the context of the Orphan Drug Act ("ODA"), which provided monetary incentives to pharmaceutical companies to develop drugs for sufficiently rare indications. Yin documents that pharmaceutical companies responded perversely to this incentive by developing drugs for "rare", ODA-qualifying subdivisions of non-rare diseases. Such perverse reactions to new government regulation is also documented in Gentry and McMichael (2020), which examines the response of device manufacturers to newly immunized products liability in response to a Supreme Court decision. Gentry and McMichael (2020) present evidence consistent with manufacturers bringing more high-risk products to market after the Supreme Court decision, seemingly in response to the change in liability regime. Against this backdrop, this paper explores the effect of differences in off-label regulation on firm incentives to submit pharmaceuticals for formal approval.

The paper proceeds as follows: Section 2 discusses our conceptual model, the regulatory background surrounding off-label use, and our empirical strategy. In particular, the section describes the policy changes enacted during the study period, and the consequent effect only on supplemental—rather than original—uses, to identify the effect of such policy changes on firm incentives. Section 3 describes the data, and Section 4 presents evidence consistent with firms strategically responding to such policy incentives. Section 5 concludes.

2 Background and Conceptual Model

2.1 Conceptual Model

The conceptual model underlying our analysis is fairly straightforward. When deciding whether to submit a use for formal approval, a firm weighs the expected costs of approval against the comparable benefits. For the first approval of a drug, the "original" approval, the benefits are extensive. Since no developed country allows for prescription of unapproved drugs, initial approval represents access to the market. If the expected sales exceed the costs of approval, a firm should file for formal approval.

After an initial submission, however, the calculus shifts. Given that most developed countries do not restrict the prescription of drugs for off-label purposes, firms can still make money off off-label uses. Rather than deciding whether to file for approval or not sell a drug, firms decide between filing for approval or leaving the use off-label (while still selling the drug). In order to continue making money on off-label uses, however, pharmaceutical companies must persuade physicians to prescribe off-label. To do this, firms generally engage in direct-to-physician promotion.[5] In countries where such promotion is illegal, companies risk large penalties for engaging in such conduct. Accordingly, such behavior is costly and reduces expected benefits of sales.

Once direct-to-physician promotion is protected, however, the cost of keeping drugs off-label declines. Accordingly, drug uses for which the benefits of approval only marginally justified the costs may no longer be submitted, as costs of approval remain the same but the expected benefits drop. This should result in a marginally lower likelihood of submitting supplemental uses for formal approval.

We exploit the general regulatory approval process in order to isolate the marginal effect of the policy changes in the US and France on pharmaceutical companies' strategic decisions.

[5] Additionally, in countries where direct to consumer promotion is legal for approved uses, pharmaceutical companies may face larger incentives to file for formal approval.

A drug typically completes 4 stages before approval:[6] The preclinical stage generally involves animal testing. Phase I includes small samples, generally testing for issues of safety. The study focuses on frequent side effects and understanding how the drug is metabolized. Phase II expands the scope to a larger group of individuals, focusing on efficacy. Comparisons between the developing drug and either a placebo or other drugs provide the basis for these controlled trials. Phase III is conducted over the largest sample, generally several hundreds to several thousands. During this stage, more information on safety and effectiveness is collected, along with information on dosages and interactions with other drugs. After Phase III, the pharmaceutical company will formally ask for approval. Given this established approval process, because we are interested in understanding a pharmaceutical company's decision to file for approval once it believes a use is viable, we condition on the date associated with Phase III status and estimate the hazard that the use is approved.[7]

Three important assumptions underlie our analysis. First, we only observe approvals and not submissions. Data on submitted-but-not-approved drug applications are not available, as the FDA has a policy of not acknowledging or disclosing such information. To accommodate this limitation, we use approval data; our results are informative of submission behavior as long as the difference over time in the number of submitted but not approved applications is equal for original and supplemental applications. We think this is a reasonable assumption given that pharmaceutical companies are repeat players and have reasonable beliefs about the approval standards.

Our second assumption is as follows: while the pre-approval process can vary across countries (i.e., pharmaceutical companies may reach different stages in different countries at different times), we treat this process as unitary. We are only interested in the difference in approval by country, not in any of the preceding steps. We do this because we are predominantly interested in the current information a company has regarding the efficacy

[6] `https://www.fda.gov/media/82381/download`

[7] The Phase III dates we extract are associated with the beginning of Phase III. However, that means that companies have general evidence of safety and effectiveness from the prior phases and are deciding whether to continue to formal approval. We drop any observations with missing Phase III dates.

of the drug. If they know that it is Phase III ready in one country, this is constructive knowledge applicable to its process in other countries.

Our identifying assumption is that the aforementioned changes in off-label regulation only affect the decision to file for supplemental approval, not the decision to file an original approval. We think this is reasonable because the restrictions on unapproved substances do not change during this period; in order for a drug to reach the market, it must receive an original approval. We use this fact to perform a simple differences-in-differences analysis, focusing on the change in US and French policy.

One potential effect of off-label regime changes, however, is that it increases the potential profits of a drug by eliminating approval costs for the supplemental use and allowing for some additional revenues from promoting the use to physicians. Insofar as this transforms a previously-unprofitable original use into a profitable one, original uses may be more likely to be submitted for approval, violating our third assumption. While this is theoretically possible, it seems empirically rare for our study. For such a case, the original use, prior to the regulatory change, is itself unprofitable. Given that the original use is more likely to receive patent protection and market exclusivity, this seems unlikely. Moreover, since off-label prescription is allowed pre-*Caronia*, the original use must be so unprofitable, that its expected plus pre-*Caronia* off-label prescription must be also unprofitable. Moreover, since none of the supplemental uses are submitted as original uses, each are individually unprofitable. Essentially, this requires that the increase in revenues from physician promotion to be sufficiently large to subsidize prior unprofitable uses (both with and without off-label prescription). This is most easily satisfied for drugs for which original plus off-label use profits were just barely negative. Since our analysis condition on reaching Phase III, the relevant changes should happen at Phase III. For supplemental uses, this is the optimal stage for this strategic decision: armed with clinical information about the supplemental use, a firm simply decides to forego filing for approval. For an original use, however, this is a late stage for a drug with otherwise-unprofitable uses to reach. While the general increase in profits

may manifest into marginal movement for previously unprofitable drugs, we expect most of this movement to occur earlier in drug development. The probability of filing conditional on reaching Phase III should not be empirically changed.

Insofar as this is not true,[8] however, this would suggest that the original approvals would not function well as a control group. To address this, we move to a triple differences model, and we capture the total increase in original approvals/decrease in supplemental approvals implied by the regulatory change.

2.1.1 Changes in United States Policy

The United States has historically allowed for off-label prescription but cracked down on direct-to-physician promotion of off-label use by pharmaceutical companies. In the United States, off-label promotion was presumptively illegal under the Food, Drug, and Cosmetic Act (FDCA).[9] The Food and Drug Administration ("FDA") considered a pharmaceutical company promoting a drug for any purpose other than that for which it received approval as a type of "misbranding," punishable by civil and criminal penalties. This interpretation continued, though years of First Amendment jurisprudence slowly chipped away at the foundations.[10] In 2012, however, a major court decision changed the expectations of liability for off-label promotion. In *United States v. Caronia*,[11] the Second Circuit Court of Appeals created a schism from prior jurisprudence, holding that truthful off-label promotion, even by pharmaceutical companies, is protected under the First Amendment. While false or inherently misleading promotion would not fall under this protection, the government did not allege that the promotion in question was either false or misleading, though there may have

[8]Notably, the violation of this assumption would be further evidence of the hypothesized sensitivity to reduced liability, making the total effect that on original and supplemental uses.

[9]Title 21 United States Code §352.

[10]Insofar as pharmaceutical companies updated their beliefs of expected liability through related litigation, we may underestimate the cumulative effect of the change in misbranding liability for off-label promotion overall.

[11]Decision of United States Court of Appeal, Second Circuit, Volume 703 Federal Reporter 3d 149 (2012).

been room to do so (Philip, 2014; Robertson, 2014).[12]

While the Second Circuit's decision was not formally binding on the entire country,[13] it did provide a credible signal to pharmaceutical companies nationwide. Following the holding, the FDA chose not to appeal the decision, signaling that it did not expect to win at the Supreme Court level. Moreover, a similar case was brought with the same holdings, further supporting the jurisprudence.[14] A recent analysis of jurisprudence following *Caronia* found that of 42 cases discussing *Caronia* in connection with off-label promotion, 22 adopted *Caronia* and 11 distinguished the case on the facts (Liu et al., 2021).[15] Accordingly, despite *Caronia* being a Circuit Court decision, the FDA's actions, and subsequent litigation, indicates that pharmaceutical companies should feel marginally more able to market off-label uses of their drugs as long as the information conveyed falls into the ambiguous category of "truthful." Insofar as marketing increases the expected market size of a given drug, *Caronia* allowed pharmaceutical companies to gain market size without incurring either approval costs or legal liability.

While there are small developments in FDA law during this period, they either affect both original and supplemental approvals or bias against our results. In 2012, the Food and

[12]Note that misbranding is not the only form of liability potentially imposed on firms related to off-label promotion. The government sometimes brings suit against pharmaceutical companies under the False Claims Act (FCA), a fraud statute that prohibits people from submitting claims for reimbursement to the government that are false or fraudulent. For off-label promotion, FCA claims allege that pharmaceutical companies fraudulently cause a claim for reimbursement to falsely be presented to the government. The specifics of these claims are unclear because most companies settle with the US government rather than take the case to trial. While there have been some changes to the interpretation and execution of FCA claims during this time, these are not targeted to off-label promotion.

If off-label liability under the FCA is otherwise unchanged during this time, our results measure the marginal effect of the change in misbranding liability for off-label promotion against the backdrop of other potential liability. If FCA liability gets more stringent, our results would be understated. If instead FCA liability for off-label promotion became more limited after *Caronia*, this most likely would be *because of Caronia* (i.e., courts may no longer allow off-label promotion to serve as a basis for the FCA claim because it is no longer considered misbranding under *Caronia*). Insofar as this is the case, this would be an indirect effect of the change in misbranding liability, which we correctly capture.

[13]Circuit opinions are only binding within the Circuit.

[14]Amarin Pharma, Inc. v. U.S. Food & Drug Admin., 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015)

[15]These distinctions followed 2 major approaches: distinguishing the procedural posture (state tort claim for compensation by injured individuals) from that of Caronia's (criminal conviction under the FDCA) or distinguishing the truthfulness of the speech (actual falsity categorically not protected by the First Amendment) from the speech at issue in *Caronia* (truthful speech). Of the 9 cases not following *Caronia*, 4 adhered to their jurisdiction's prior holding (Liu et al., 2021).

Drug Administration Safety and Innovation Act (FDASIA) added another track for priority review: breakthrough therapy designation. However, this status applied to both original and supplemental approvals.[16] In 2016, Congress passed The Medical Cures Act, which broadened the type of evidence that could be submitted as part of a drug application.[17] According to the FDA "real world evidence can be generated by different study designs or analyses, including but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective)."[18] Insofar as real-world evidence reduces the cost of approval, this could make filing for formal approval marginally more attractive after 2016. Theoretically, real-world evidence may be more likely to be used to support supplemental uses because it would be easier to collect real-world evidence after an initial approval. Insofar as this decline in cost is bigger for supplemental uses, this should only bias against our hypothesized effect of fewer supplemental submissions after *Caronia*.

With this newfound ability to market uses that remain off-label, a major concern emerges as to why pharmaceutical companies should try to submit supplemental uses for formal approval. When off-label promotion was illegal, the ability to openly and freely disperse information remained a major reason to undertake this cost. With this distinction eroding, pharmaceutical companies may be marginally less likely to incur the cost of supplemental approval and leave new uses off-label.

[16]In 2019, 26 uses were approved through the breakthrough therapy designation, 12 of which were supplemental uses. `fda.gov/media/95302/download`.

[17]The statute provides that "The Secretary shall establish a program to evaluate the potential use of real world evidence— "(1) to help to support the approval of a new indication for a drug approved under section 505(c); and "(2) to help to support or satisfy postapproval study requirements" 21 U.S.C. 355g. The section allows for real world evidence to be used in other contexts as well, at the Secretary's discretion and notes that this should not be construed as changing the standards of period for consideration or grounds for refusing or approving an application.

[18]`https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence`

2.1.2 Changes in French Policy

During recent years, France has experienced its own change in policy regarding off-label prescription. Prompted by the Mediator scandal, in which a diabetes drug caused sometimes-fatal valvular heart disease, France passed a law in December 2011 aimed at monitoring off-label prescriptions (Emmerich et al., 2012). The "Temporary Recommendations for Use" ("TRUs") decree established a process for limiting off-label use and temporarily supervising prescriptions for off-label indications. The objective of the process was to open an observation window (maximum of three years) in order to assess the benefits and risks of marketed drugs for off-label indications. Pharmaceutical companies bore the responsibility to track prescriptions of their drugs with a TRU and report any unusual prescriptions. The issuance of a TRU also depended on the inherent safety of the drug, quality of existing scientific information, and the severity of the illness (Emmerich et al., 2012). After the French government realized that being too restrictive on regulation of off-label prescriptions creates financial cost, France amended the policy in 2014 to allow a TRU to be issued even if a therapeutic alternative is available, as long as the alternative does not share the active substance, dosage, and form. Similarly, the ability to prescribe was broadened slightly.

While the proposed regulation was theoretically restrictive, the institution of the TRU regime had ambiguous effects on off-label prescriptions. The regime still acknowledged a physician's ability to prescribe off-label for specific patients, though it aimed to limit such prescription (Emmerich et al., 2012). The regulation itself seemed to both increase and decrease off-label prescription. Anticipated effects were mixed: one scholar opines that the TRU worked to liberalize off-label policy (Degrassat-Théas et al., 2015) while another scholar anticipated that off-label use would be restricted because "the off-label prescription rules will be binding for physicians and could restrict access to off-label drugs by patients as their reimbursement will be restricted."

Empirical evidence on this policy has suggested that prescribers largely ignored TRUs in their prescription patterns. While very few drugs have actually received TRUs (Degrassat-

Théas et al., 2015),[19] off-label prescription has not seemed to drop considerably. A survey of twenty-three general practitioner offices in France in 2015-2016 found that 18.5% of drug prescriptions were for off-label purposes (Drogou et al., 2019). The study noted that the TRUs were "intended for specific groups of patients and rare diseases, and does not really concern [general practitioners]." Similarly, a 2015 survey studied pharmacists' understanding of the prescription of baclofen for alcohol dependence, the first TRU to be issued (in 2014) (Auffret et al., 2018). The survey found that despite 81% of the pharmacists knowing that the TRU had been issued for baclofen, 65.7% of responding pharmacists had never seen "TRU" written on the prescription. Despite this, the pharmacists continued to dispense the drug. The same study noted that including patients in a TRU is often burdensome for practitioners, who continue to prescribe the off-label use without monitoring the patients.

If physicians largely did not change prescription habits in response to TRUs, pharmaceutical companies may rationally leave their submission strategy unchanged. Indeed, insofar as the TRU allows an additional three-year observation window, pharmaceutical companies may choose to postpone formal approval (Degrassat-Théas et al., 2015). This effect, however, will be more difficult to isolate, given France's relatively small impact on global pharmaceutical sales. This exercise presents a first pass at estimating sensitivities over the full sample of drugs.

2.2 Empirical Strategy

Our main specification is a difference-in-difference hazard rate model of approval

$$h(t)_{id} = h_0(t)exp(X'\beta) \tag{1}$$

[19]Indeed, only 3 drugs received TRUs by the end of 2014 (Covington and Burling, 2015).

such that

$$X'\beta = \delta_i + \alpha_t + \beta_0 X_t^i + \beta_1 X_t^d + \beta_2 Supplemental_{idt} + \beta_3 OLDU_t + \beta_4 Supplemental_{idt} \times OLDU_t \tag{2}$$

where $Supplemental_{idt}$ is an indicator variable for whether the use of drug d for indication i in year t is considered supplemental. $OLDU$ is a generalization of either Off-Label Drug Use (OLDU) regulatory change, *Caronia* in the US or TRU in France. $Caronia_t$ is an indicator for whether t is after the *Caronia* holding,[20] and TRU_t is an indicator for whether t falls after the TRU regime was passed. Because these specifications only consider changes within the US or France, no country interactions are necessary. With X_t^i we control for disease indication-time specific variables such as the prevalence of disease i in year t in the country or the competition level in the market of disease i in year t. X_t^d stands for drug-time specific variation such as patent life of drug substance d. We also include indicator variables for year t, and ICD classification of the indication i under study.[21] Prevalence of disease i controls for the potential market size of such indication in the country, which is likely to positively affect approval. The coefficient of the interaction of the indicator variable $Supplemental_{idt}$ with the dummy variable of the regulatory change should identify the relative impact of the policy change on the hazard of approval of supplemental indications.

In contexts considering comparisons across countries, c, we move to a triple difference model:

$$\begin{aligned} X'\beta = \delta_i + \gamma_c + \alpha_t + \beta_0 X_{ct}^i + \beta_1 X_t^d + \\ \beta_2 Supplemental_{idct} + \beta_3 OLDU_t + \beta_4 Supplemental_{idct} \times OLDU_t + \\ \beta_5 Supplemental_{idct} \times ChangeCountry + \beta_6 OLDU_t \times ChangeCountry + \\ \beta_7 Supplemental_{idct} \times OLDU_t \times ChangeCountry \end{aligned} \tag{3}$$

[20] *Caronia* came down on December 3, 2012.

[21] Each observation is associated with a specific indication; however, for the sake of estimating fewer fixed effects, we aggregate these indications into broader ICD codes.

where $OLDU_t$ again refers the period of time corresponding to either $Caronia_t$ or TRU_t and $ChangeCountry$ is an indicator for the country of the policy change, either US or France. Note that $Caronia_t$ and TRU_t are constructed as in equation (2) and are interacted with the relevant country of change. γ_c is a country-specific fixed effect. X_{ct}^i represents indication-country-time specific variables such as the prevalence of disease i in country c and year t. The parameter β_7 signifies the relative change between original and supplemental approvals in US/France after *Caronia*/TRU relative to the comparable change in the difference between original and supplemental approvals in other countries.

3 Data and Descriptive Statistics

3.1 Research and Development Data

The main source of data is from Citeline, Informa Pharma Intelligence.[22] This data lists the unique drug products for companies engaging in research and development. For each drug substance, we observe the diseases ("indications") for which it is being developed, the status of each disease worldwide, and key events in the development process. Using a string-processing algorithm, we use the data to estimate the dates of approval for each disease for a sample of countries. A full description of the data fields provided by Citeline, and the specific process by which we use these to produce indication-country specific dates, are outlined in the Data Appendix.

Using this data and algorithm, we construct a dataset in which a single observation is a unique drug-indication-country entry. Only observations with non-missing Phase III dates are retained. We limit observations to those with Phase III dates between 2000 and the date of download (February 2019). For countries who are members of the EU, we impute EU dates if they precede the national dates of approval.[23]

[22]This data was downloaded in February 2019.

[23]This data also provides information on whether a drug obtained a expedited review designation or orphan drug status. We consider these designations granted if the date associated with them is not missing.

In order to operationalize this rich data, we crosswalk the indications listed in Citeline to ICD-10 codes.[24] We do this through a mixture of automated string matching and manual matching. This allows us to control for differences in hazard of approval by broad disease categories.

3.2 Drug Classification

In order to account for differences in hazard of approval by drug characteristics, we use 3 strategies. First, we group based on generic names using the International Nonproprietary Names (INN) stems and prefixes established by the World Health Organization. While a nonproprietary name could belong to more than one category, based on prefixes and stems, we only place it in one category. Where no generic name was available[25] we crosswalk based on listed mechanism of action to generic stems.

The second and third approaches involve principal factor analysis to reduce a set of nonexclusive indicator variables into a smaller number of factors using therapeutic class and mechanism of action, respectively. Therapeutic class categorizes the type of pathologies each drug is meant to treat, and a drug substance can be associated with multiple therapeutic classes. For mechanism of action, we simplify the listed mechanism of actions into groups corresponding to the type of enzyme targeted by the compound as well as information about the systems it affects.[26] This still leaves us with a large number of indicator variables.[27] Using these indicator variables, we perform a principal component analysis to condense the variation in therapeutic class and the mechanism of action indicators into 30 and 40 factors, respectively. The following analysis uses each of the three approaches to control for differences in drug substance.

[24]Some of the interactions could not be matched to a broad ICD code. These are retained in the following analysis, under an "Unassigned" ICD category.

[25]Sometimes a drug is too preliminary or only have alphanumeric names.

[26]We group mechanism of actions into the type of ezyme targeted (without considering whether it is an antagonist or agonist).

[27]We do not include mechanism of action categories that apply to five or less drug entities to preserve degrees of freedom.

3.3 Competition Data

To control for potential competitors in a given indication, we use the Citeline data itself. Relevant competition is a very difficult measure to capture, as new markets are not always precisely defined. Our measure of competition is denoted by the number of substances each year that reaches Phase III in a given ICD category.[28] We then merge this data into the Citeline data by year and ICD group. This is a much more detailed measure of competition than can be found outside of the data, as we observe development of specific indications (rather than therapeutic classes, which do not always line up with indication). By only looking at indications reaching Phase III, we cull some noise of experimentation. This measure of competition necessarily assumes that firms are aware of projects that competitors have in the pipelines. Given the level of repeated play between pharmaceutical companies and that they usually have access to Citeline data, we think this is a reasonable assumption.

3.4 Disease Prevalence

The decision to file for formal approval depends on the expected market size for a drug (Acemoglu and Linn, 2004; Dubois et al., 2015). For a sufficiently large market, it may make more sense to incur the costs of formal approval, all else being equal. To capture a measure of the prevalence of the disease targeted, we incorporate data from the Institute for Health Metrics and Evaluation at the University of Washington. We use their Global Health Data Exchange[29] tool to collect information on disease prevalence. We then use string and manual matching to associate this information with the indications in the Citeline data. Since the GHD data is less detailed than the indications in the Citeline data, we classify each indication as falling within broader GHD disease categories.[30] While we would ideally prefer a more detailed measure of prevalence, the broad categories provide a measure of potential

[28] We represent this value in terms of hundreds for ease of coefficient interpretation.

[29] This data was downloaded on March 2021 from `http://ghdx.healthdata.org/gbd-results-tool`. The data is available from 1990 to 2019.

[30] Specifically, we group indications as falling within the level 2 classification of causes in the GHD data.

use, while ensuring that all indications are on the same playing field.

For our prevalence measure, we use nominal prevalence data, defined as the total number of cases in the population.[31] We chose this measure because it not only gives the relative importance of the disease within the country but also provides a sense of the cross-country relative size of affected population. If a country has a large population but a small incidence of the disease, pharmaceutical companies may value the country's regulations less strongly. Conversely, even if a country is relatively small, if it has a sizeable affected population, a pharmaceutical company may choose to file for formal approval, given country regulations.

In addition to the GHD data, we also incorporate data on mortalities from the World Health Organization (WHO). As number of mortalities captures the most severe impact of a given indication, this should supplement the prevalence data. The data uses deaths from national vital registration systems and lists the causes of deaths for various age groups and sex. We use the death count for all ages and sexes for a country in a given year.[32] For some countries, some years of data are missing. In order to account for this, we impute the prevalence of the most recent preceding year. The availability of this data varies by year, country, and level of ICD detail. Using our indication-ICD code crosswalk, we crosswalk indications to any 3-digit ICD code associated with it. Our program aggregates deaths across the range of ICD codes associated with each indication.

3.5 Patent Expiration

The remaining time on a given patent can affect a firm's decision process. If the firm feels that the supplemental use can create additional patent rights, a shortened time to expiration may spur a company to file for supplemental approval. Conversely, when more time remains on the patent, supplemental approval may not be necessary to maintain exclusivity. We use data from the PAIR database (Public Patent Application Information Retrieval of US Patent and Trademark Office) and match it to US patents listed in Citeline. Taking the latest filing

[31] We represent this value in billions for ease of coefficient interpretation.
[32] We represent this value in hundreds of thousands for ease of coefficient interpretation.

date as the relevant filing date, we approximate the expiration date as twenty years after. We then use days until patent expiration[33] as a control. Once the patent expiration occurs, this values becomes zero (as does any observation with no patent associated with it).

3.6 Descriptive Statistics

Table 1 presents some basic descriptive statistics regarding approved drugs across country and year. Columns (1), (4), and (7) of Table 1 reports approval statistics across different countries during the period 2000-2018. Total number of approvals are the highest in the US, and the fewest number of approvals and drugs are in Australia. The average number of supplemental indications per drug ranges from 0.22 in France to 0.45 in the United States, suggesting that many drugs do not get a supplemental approval.

Table 1 also breaks out these averages by time periods, 2000-2012 and 2013-2018. Comparing the average supplemental approvals per drug across columns show a drop in supplemental approvals for the United States. A comparable drop is not seen for Australia and is quite small for France. These data are simply suggestive, however. The following section displays results for the full models.

[33]For any given date interval in our data, we subtract the date from the expiration date, creating a "days until expiration" measure. We represent this value in terms of thousands for ease of coefficient interpretation.

Table 1: Descriptive Statistics (2000-2012, 2013-2018)

	United States			France			Australia		
	All	2000-2012	2013-2018	All	2000-2012	2013-2018	All	2000-2012	2013-2018
Total approvals	2006	1048	958	1626	869	757	998	521	477
Original approvals	1589	806	783	1470	789	681	902	475	427
Supplemental approvals	417	242	175	156	80	76	96	46	50
Supp. approvals per drug (ave.)	.45	.54	.34	.22	.23	.21	.23	.22	.23

Notes: The table lists approvals by type and country. Because sometimes an original application contains multiple indications, original approvals can be bigger than approved drugs.

4 Results

In this section, we present the results of a proportional hazard model, both a weibull parametric model and a cox proportional model. Each model imposes a different assumption on the baseline hazard function, so the results are interesting to compare. This analysis models the hazard of failure, which in this context is formal approval. The coefficients reported are hazard ratios, which are the ratios of the hazard rates with and without a given variable. A hazard ratio greater than one indicates that the variable is associated with a higher rate of failure (formal approval), while a ratio less than one is associated with a lower rate of failure.[34]

The survival analysis allows us to estimate the differential effect of off-label regulation on the hazard rate. The hazard rate analysis allows for an origin and endpoint. The origin for all observations is the Phase III date, and the endpoint is either the end of the sample period or the approval date. Failure in this model is indicated when the observation is approved. Any approval date that was subsequent to the download data was treated as not having been approved by the end of observation.

To achieve time-varying treatment, we split the data in two ways, allowing a different proportional hazard ratio for these periods. The first split occurs at the first failure (approval) for a drug substance. Prior to the first approval, any extant use could be considered the "original" use and none could be used off-label. Once a use receives approval, all subsequent uses (extant or future) are considered supplemental. Accordingly, supplemental status is a dynamic concept linked directly to the ability to legally sell the drug for some purpose. This definition of supplemental requires fewer assumptions about uses always being known as supplemental uses - uses may be treated similarly until the first approval.

The second time-varying treatment is by year. We split the survival time into year-long

[34]The standard errors are calculated using the delta method, but the p-values are calculated from the natural regression coefficients (i.e., if a coefficient is significantly different than zero). While tests based on the hazard ratio would be asymptotically equivalent to one based on the underlying coefficient, the hazard ratio has a more skewed distribution in real samples.

intervals, allowing covariates—such as competition, patent duration, etc.—to vary by year. This allows us to estimate a different proportional hazard ratio for each subperiod. These splits also allows us to designate *Caronia* as years 2013 onward and the *TRU* as year 2012 onward.[35] Because we include a full set of year indicator variables, however, we do not report the main effects for *Caronia* or *TRU* in the following results, as it is not meaningful. The difference-in-difference model accordingly follows equation (2); however, given that we split our units of observations, we can have multiple intervals of time for each drug-indication-country unit.[36]

4.1 US Results

4.1.1 US Within-Country Analysis

The simplest comparison is within a single country. By looking at the change in the relative hazard rate between original and supplemental approvals, we start by looking only within the US. Here, the variable of interest is $Caronia \times Supplemental$, which we expect will be associated with a lower proportional hazard of approval. For the survival analysis, this means that the hazard ratio to failure (approval) should be significantly less than one. The results are listed in Table 2. The columns vary by the type of model used—indicated by the last row—as well as the method by which we control for drug substance characteristics, indicated by the fourth, fifth, and sixth rows.

[35] The holding of *Caronia* came down in December 2012 and the TRU was passed in December 2011.

[36] For this reason, the observations reported are the number of split intervals, not indication-drug-country units.

Table 2: Proportional Hazard Model for Approval: Caronia, Within-Country

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Supplemental	4.269***	3.895***	4.311***	4.386***	4.110***	3.775***	4.196***	4.166***
	(0.907)	(0.797)	(0.936)	(0.967)	(0.864)	(0.786)	(0.900)	(0.903)
Supplemental x Caronia	0.608***	0.528***	0.584***	0.575***	0.691**	0.569***	0.651**	0.658**
	(0.094)	(0.073)	(0.101)	(0.096)	(0.114)	(0.088)	(0.120)	(0.119)
Observations	57,222	57,222	57,222	57,222	57,222	57,222	57,222	57,222
Generic Group Indicators		x				x		
Therapeutic Class Factors			x				x	
Mechanism of Action Factors				x				x
Model	Weibull	Weibull	Weibull	Weibull	Cox	Cox	Cox	Cox

Notes: Reported effects are hazard ratios. Other variables included but not reported are indicator variables for year and icd group. Standard errors clustered by icd group. Significance levels: *** p<0.01, ** p<0.05, * p<0.1.

Caronia × *Supplemental* is associated with a hazard ratio significantly less than one, multiplicatively lowering the hazard rate of formal approval for supplemental uses after *Caronia*, relative to the comparable effect on original uses. The magnitude of this effect ranges from 0.528 in column (2) to 0.691 in column (5).

Table 3: Proportional Hazard Model for Approval: Caronia, Within-Country

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Supplemental	6.338***	6.326***	6.041***	7.125***	6.044***	6.270***	5.895***	6.745***
	(1.423)	(1.799)	(1.461)	(1.742)	(1.351)	(1.766)	(1.399)	(1.601)
Supplemental x Caronia	0.463***	0.362***	0.466***	0.406***	0.523***	0.382***	0.514***	0.457***
	(0.074)	(0.072)	(0.086)	(0.078)	(0.091)	(0.085)	(0.101)	(0.094)
Remaining Patent Days/1000	1.163***	1.166***	1.170***	1.168***	1.153***	1.162***	1.162***	1.161***
	(0.016)	(0.017)	(0.017)	(0.015)	(0.016)	(0.017)	(0.017)	(0.016)
Suppl. x Remaining Patent Days/1000	0.829***	0.823***	0.848***	0.808***	0.836***	0.818***	0.849***	0.813***
	(0.027)	(0.037)	(0.027)	(0.025)	(0.026)	(0.036)	(0.025)	(0.024)
Expedited Review Designation	2.413***	2.325***	2.350***	2.514***	2.081***	1.991***	2.018***	2.164***
	(0.302)	(0.320)	(0.276)	(0.316)	(0.243)	(0.273)	(0.227)	(0.262)
Orphan Drug Act Status	1.157	0.979	1.180	1.140	1.125	0.956	1.159	1.110
	(0.167)	(0.151)	(0.182)	(0.172)	(0.158)	(0.148)	(0.174)	(0.167)
Competition/100	1.081	0.921	0.889	1.293	1.799	1.469	1.332	2.196
	(1.585)	(1.404)	(1.307)	(1.889)	(2.685)	(2.272)	(1.990)	(3.275)
Competition/100 Squared	2.362	3.409	2.853	1.529	0.915	1.289	1.399	0.523
	(7.097)	(10.624)	(8.643)	(4.604)	(2.806)	(4.091)	(4.333)	(1.611)
Mortality/100k	1.128	1.044	1.065	1.125	1.088	1.001	1.030	1.084
	(0.243)	(0.174)	(0.168)	(0.228)	(0.185)	(0.145)	(0.135)	(0.178)
Supplemental x Mortality/100k	1.275***	1.310***	1.296***	1.254***	1.317***	1.326***	1.323***	1.296***
	(0.080)	(0.099)	(0.080)	(0.079)	(0.088)	(0.098)	(0.087)	(0.088)
Observations	57,222	57,222	57,222	57,222	57,222	57,222	57,222	57,222
Generic Group Indicators		x				x		
Therapeutic Class Factors			x				x	
Mechanism of Action Factors				x				x
Model	Weibull	Weibull	Weibull	Weibull	Cox	Cox	Cox	Cox

Notes: Reported effects are hazard ratios. Other variables included but not reported are indicator variables for year, icd group, and missing mortality data (with interactions). Standard errors clustered by icd group. Significance levels: *** p<0.01, ** p<0.05, * p<0.1.

Table 3 presents the same models as Table 2, including other control variables such as patent protection, competition, and prevalence. For the main variables of interest, $Supplemental \times Caronia$, the coefficients are uniformly significantly less than 1, indicating that the hazard rate of formal approval declines post-Caronia relative to the rate for original uses. The other control variables are similarly interesting. While the effect of $Competition$ is largely insignificant across all specifications, this is potentially because competitive pressures are more likely to be important at earlier stages of development. $RemainingPatentDays$ is significantly greater than one, suggesting a higher hazard of approval with days remaining on-patent.[37] $RemainingPatentDays \times Supplemental$ is significantly less than one, suggesting that relative to original uses, remaining time reduces the proportional hazard of filing for supplemental approval. This can be consistent with firms strategically using supplemental formal approvals to retain some level of exclusivity.

We also include indicator variables for whether a drug has received an expedited review or orphan drug designation. $ExpeditedReviewDesignation$ is uniformly significantly greater than 1, consistent with theory. $OrphanDrugActStatus$ is more noisy and less precise.

Finally, our measure of market size is $Mortality$ and $Supplemental \times Mortality$, which represents the prevalence of the most severe consequences of a disease in a given country and year. While $Mortality$ is indistinguishable from one, $Supplemental \times Mortality$ is significantly greater than one, indicating that the relationship of market size to approval may depend on severity of the disease consequences, particularly for supplemental uses.

[37] Notably, given that the measure is in thousands of days, however, this is a very small effect.

Table 4: Proportional Hazard Model for Approval: Caronia, Within-Country

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Supplemental	8.462***	8.906***	7.957***	9.372***	7.928***	8.554***	7.555***	8.553***
	(2.540)	(3.134)	(2.442)	(3.002)	(2.376)	(2.965)	(2.312)	(2.644)
Supplemental x Caronia	0.483***	0.381***	0.489***	0.420***	0.553***	0.403***	0.544***	0.477***
	(0.076)	(0.078)	(0.090)	(0.081)	(0.095)	(0.093)	(0.107)	(0.098)
Remaining Patent Days/1000	1.163***	1.166***	1.170***	1.168***	1.153***	1.162***	1.161***	1.161***
	(0.016)	(0.017)	(0.017)	(0.016)	(0.016)	(0.017)	(0.017)	(0.016)
Suppl. x Remaining Patent Days/1000	0.830***	0.818***	0.850***	0.806***	0.837***	0.814***	0.852***	0.813***
	(0.027)	(0.038)	(0.027)	(0.025)	(0.026)	(0.037)	(0.026)	(0.024)
Expedited Review Designation	2.452***	2.360***	2.387***	2.558***	2.107***	2.026***	2.045***	2.198***
	(0.299)	(0.315)	(0.273)	(0.311)	(0.242)	(0.272)	(0.224)	(0.261)
Orphan Drug Act Status	1.125	0.951	1.151	1.110	1.099	0.931	1.133	1.085
	(0.167)	(0.150)	(0.182)	(0.175)	(0.159)	(0.147)	(0.174)	(0.169)
Competition/100	1.093	0.967	0.901	1.285	1.866	1.572	1.392	2.233
	(1.597)	(1.489)	(1.321)	(1.863)	(2.775)	(2.445)	(2.074)	(3.309)
Competition/100 Squared	2.319	3.192	2.779	1.527	0.833	1.136	1.258	0.484
	(6.937)	(10.009)	(8.388)	(4.566)	(2.552)	(3.613)	(3.891)	(1.486)
Prevalence (Billions)	3.827	2.959	4.949	9.750**	3.447	2.553	4.261	7.982**
	(3.676)	(3.941)	(6.569)	(9.994)	(3.170)	(3.169)	(5.498)	(7.647)
Supplemental x Prevalence	0.014	0.007	0.013	0.021	0.017	0.012	0.020	0.034
	(0.038)	(0.023)	(0.040)	(0.053)	(0.047)	(0.038)	(0.062)	(0.086)
Observations	57,222	57,222	57,222	57,222	57,222	57,222	57,222	57,222
Generic Group Indicators		x				x		
Therapeutic Class Factors			x				x	
Mechanism of Action Factors				x				x
Model	Weibull	Weibull	Weibull	Weibull	Cox	Cox	Cox	Cox

Notes: Reported effects are hazard ratios. Other variables included but not reported are indicator variables for year, icd group, and missing prevalence data (with interactions). Standard errors clustered by icd group. Significance levels: *** p<0.01, ** p<0.05, * p<0.1.

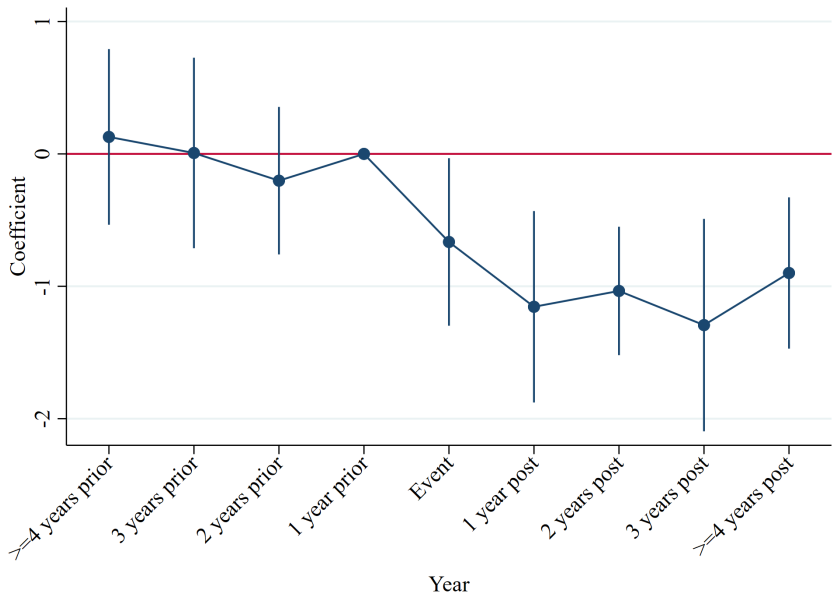

Figure 1: Event Study: Caronia

Notes: The coefficients plotted in the figure follow the specification in Table 3, column (2), with period indicator variables replacing *Caronia*. The interactions of *Caronia* and period indicators are plotted in the figure, with a 95% confidence interval. Standard errors are clustered by icd group. Significance levels: *** p<0.01, ** p<0.05, * p<0.1.

Table 4 performs the same analysis as Table 3, except that it substitutes *Prevalence*, the nominal prevalence of a disease in a given country and year, for the number of deaths. This variable is largely insignificant, as is its interaction with *Supplemental* status. This insignificance is likely due to the very crude disease classifications available in the data. All the rest of the coefficients follow similar patterns as in Table 3.

Finally, in order to test the parallel trends assumption for the difference-in-differences specification, we perform an event study. *Caronia* is decomposed into a series of time indicator variables, with year 2013 designated as the "event year" and the year prior as the baseline period. Figure 1 plots the coefficients[38] for the interaction effects for these periods, representing the change relative to the baseline period. The interaction effects leading up to *Caronia* have coefficients close to zero and statistically insignificant. As we would expected with an exogenous shock, the effects for the event and subsequent periods are negative and

[38]The plotted effects are coefficients, not hazard ratios, so the baseline is zero. Hazard ratios can be obtained by the exponent of the coefficient.

significant.

4.1.2 US Cross-Country Comparisons

The prior analyses have only considered changes within the US, relying on the fact that the regulatory changes only affect supplemental uses, not original uses. Insofar as *Caronia* affects original uses, a cross-country comparison addresses this.

Table 5: Proportional Hazard Model for Approval: Caronia, Cross-Country Comparison with Australia

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Supplemental	2.294***	2.074***	2.130***	2.319***	2.250***	2.095***	2.107***	2.247***
	(0.403)	(0.368)	(0.381)	(0.393)	(0.407)	(0.380)	(0.384)	(0.392)
Caronia	0.208**	0.118***	0.184**	0.191**	0.134***	0.090***	0.123***	0.126***
	(0.153)	(0.086)	(0.135)	(0.140)	(0.099)	(0.065)	(0.091)	(0.093)
Supplemental x Caronia	0.952	0.854	0.930	0.845	1.113	0.946	1.063	1.013
	(0.232)	(0.185)	(0.216)	(0.206)	(0.278)	(0.216)	(0.255)	(0.253)
US	2.308***	2.527***	2.351***	2.330***	2.335***	2.565***	2.373***	2.358***
	(0.202)	(0.227)	(0.204)	(0.208)	(0.201)	(0.228)	(0.203)	(0.207)
Supplemental x US	1.827**	1.562*	1.875**	1.820**	1.773**	1.490	1.826**	1.764**
	(0.476)	(0.394)	(0.491)	(0.470)	(0.468)	(0.387)	(0.481)	(0.462)
Caronia x US	0.956	0.981	0.954	0.960	0.937	0.960	0.933	0.939
	(0.119)	(0.130)	(0.115)	(0.119)	(0.115)	(0.124)	(0.110)	(0.115)
Supplemental x Caronia x US	0.628	0.660*	0.626*	0.669	0.601*	0.630*	0.602*	0.627
	(0.180)	(0.166)	(0.176)	(0.192)	(0.178)	(0.170)	(0.176)	(0.188)
Observations	120,994	120,994	120,994	120,994	120,994	120,994	120,994	120,994
Generic Group Indicators		x				x		
Therapeutic Class Factors			x				x	
Mechanism of Action Factors				x				x
Model	Weibull	Weibull	Weibull	Weibull	Cox	Cox	Cox	Cox

Notes: Reported effects are hazard ratios. Other variables included but not reported are indicator variables for year and icd group. Standard errors clustered by country-icd group pairs. Significance levels: *** p<0.01, ** p<0.05, * p<0.1.

Table 6: Proportional Hazard Model for Approval: Caronia, Cross-Country Comparison with Australia

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Supplemental	3.356***	3.132***	3.023***	3.489***	3.292***	3.248***	3.021***	3.426***
	(0.636)	(0.652)	(0.581)	(0.605)	(0.646)	(0.692)	(0.592)	(0.613)
Caronia	0.289	0.186**	0.256*	0.288*	0.190**	0.145**	0.174**	0.195**
	(0.220)	(0.141)	(0.193)	(0.218)	(0.146)	(0.111)	(0.132)	(0.149)
Supplemental x Caronia	0.757	0.650*	0.768	0.642*	0.883	0.706	0.870	0.764
	(0.196)	(0.151)	(0.189)	(0.168)	(0.237)	(0.173)	(0.221)	(0.205)
US	2.316***	2.593***	2.374***	2.336***	2.368***	2.668***	2.422***	2.394***
	(0.207)	(0.242)	(0.211)	(0.214)	(0.209)	(0.243)	(0.212)	(0.215)
Supplemental x US	1.790**	1.618*	1.780**	1.901**	1.725**	1.527	1.724**	1.827**
	(0.452)	(0.415)	(0.462)	(0.482)	(0.443)	(0.399)	(0.450)	(0.468)
Caronia x US	0.883	0.905	0.881	0.884	0.858	0.877	0.855	0.857
	(0.115)	(0.126)	(0.113)	(0.115)	(0.111)	(0.119)	(0.108)	(0.111)
Supplemental x Caronia x US	0.606*	0.595*	0.610*	0.624	0.577*	0.571**	0.585*	0.575*
	(0.173)	(0.158)	(0.173)	(0.183)	(0.173)	(0.163)	(0.174)	(0.177)
Remaining Patent Days/1000	1.150***	1.153***	1.159***	1.153***	1.144***	1.152***	1.153***	1.149***
	(0.013)	(0.014)	(0.014)	(0.013)	(0.013)	(0.014)	(0.014)	(0.013)
Suppl. x Remaining Patent Days/1000	0.837***	0.831***	0.858***	0.818***	0.841***	0.826***	0.856***	0.819***
	(0.026)	(0.036)	(0.026)	(0.024)	(0.025)	(0.035)	(0.025)	(0.024)
Expedited Review Designation	2.372***	2.265***	2.319***	2.469***	2.080***	2.010***	2.031***	2.162***
	(0.298)	(0.322)	(0.278)	(0.305)	(0.246)	(0.281)	(0.234)	(0.257)
Orphan Drug Act Status	1.288*	1.066	1.261	1.289*	1.261*	1.060	1.257	1.261
	(0.180)	(0.162)	(0.179)	(0.184)	(0.174)	(0.162)	(0.176)	(0.182)
Competition/100	2.861	2.496	2.475	3.317	4.061	3.556	3.058	4.761
	(3.467)	(3.143)	(3.063)	(4.016)	(5.015)	(4.513)	(3.828)	(5.917)
Competition/100 Squared	0.045	0.054	0.051	0.030	0.022	0.024	0.033	0.014
	(0.150)	(0.188)	(0.172)	(0.101)	(0.076)	(0.085)	(0.114)	(0.047)
Mortality/100k	1.010	0.988	0.991	1.015	0.999	0.979	0.981	1.002
	(0.073)	(0.053)	(0.055)	(0.070)	(0.064)	(0.049)	(0.050)	(0.062)
Supplemental x Mortality/100k	1.260***	1.265***	1.290***	1.232***	1.294***	1.279***	1.309***	1.256***
	(0.079)	(0.099)	(0.082)	(0.082)	(0.086)	(0.097)	(0.088)	(0.088)
Observations	120,994	120,994	120,994	120,994	120,994	120,994	120,994	120,994
Generic Group Indicators		x				x		
Therapeutic Class Factors			x				x	
Mechanism of Action Factors				x				x
Model	Weibull	Weibull	Weibull	Weibull	Cox	Cox	Cox	Cox

Notes: Reported effects are hazard ratios. Other variables included but not reported are indicator variables for year icd group, and missing mortality data (with interactions). Standard errors clustered by country-icd group pairs. Significance levels: *** p<0.01, ** p<0.05, * p<0.1.

Extending this analysis to include comparisons to other countries requires moving to a full triple differences set-up, as specified in equation (3). Choosing the correct countries, however, is important. For the US, we choose Australia because of its similarity to the US in terms of regulatory authority and culture.

Tables 5 display the results of the triple difference for *Caronia*, and Table 6 displays the results controlling for competition, patent protection, and market size. The parameter of interest is the coefficient on $US \times Caronia \times Supplemental$, which is consistently around 0.6 in both tables. This estimate is statistically significant for 5 of the 8 in Table 5, and the estimate precision increases as control variables are added in Table 6. Not only is the treatment effect as expected, but the control variables also present intuitive effects consistent with prior tables. The effect of $RemainingPatentDays$ is the same as in prior tables, as is the effect of $Mortality$.

Results are consistent with firm sensitivity to changes in costs of off-label regulation characterized by *Caronia*. The lower cost associated with promoting off-label uses lowers the hazard of supplemental approval, relative to original approvals—across a variety of specifications. Further, insofar as original uses do not provide a good control group, our cross-country analysis shows that the difference in hazard between supplemental and original uses is significantly different in the US relative to the comparable difference in Australia over this period.

4.2 France Results

Turning to France's TRU process, we perform the same difference-in-differences analysis. The construction of the data for the survival models is described above.[39] As noted above, while the regulation was intended to restrict off-label prescription—and accordingly, increase the benefits of formal approval—it was largely ignored by physicians. Weak enforcement could either lead to no response from pharmaceutical companies or to even extending time

[39]This section only presents Cox proportional models, as the Weibull parametric models had highly singular or nonsymmetric variance matrices.

Table 7: Proportional Hazard Model for Approval: TRU, Within-Country

Variables	(1)	(2)	(3)	(4)
Supplemental	1.564**	1.395	1.345	1.619**
	(0.349)	(0.335)	(0.343)	(0.370)
Supplemental x TRU	1.389	1.023	1.388	1.280
	(0.322)	(0.262)	(0.352)	(0.310)
Observations	59,253	59,253	59,253	59,253
Generic Group Indicators		x		
Therapeutic Class Factors			x	
Mechanism of Action Factors				x
Model	Cox	Cox	Cox	Cox

Notes: Reported effects are hazard ratios. Other variables included but not reported are indicator variables for year and icd group. Standard errors clustered by icd group. Significance levels: *** p<0.01, ** p<0.05, * p<0.1.

until approval, as the delay is essentially sanctioned by the French government.

Tables 7-8 only examine behavior within France. Table 7 incorporates the most parsimonious specification. The parameter of interest, $Supplemental \times TRU$, is statistically insignificant, finding no effect of the TRU on supplemental drug approval.

Table 8: Proportional Hazard Model for Approval: TRU, Within-Country

Variables_x	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Supplemental	1.447	1.202	1.196	1.539	1.521*	1.279	1.237	1.661**
	(0.410)	(0.341)	(0.358)	(0.455)	(0.364)	(0.330)	(0.338)	(0.421)
Supplemental x TRU	1.430	1.077	1.491	1.249	1.442	1.084	1.498	1.270
	(0.335)	(0.280)	(0.378)	(0.315)	(0.339)	(0.283)	(0.377)	(0.323)
Competition/100	84.199**	78.661**	60.713**	82.301**	85.823**	79.878**	62.147**	83.982**
	(165.985)	(159.972)	(118.111)	(162.725)	(169.198)	(161.494)	(120.771)	(166.191)
Competition/100 Squared	0.000**	0.000**	0.000*	0.000**	0.000**	0.000**	0.000**	0.000**
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Remaining Patent Days/1000	1.069***	1.071***	1.073***	1.083***	1.069***	1.072***	1.074***	1.083***
	(0.015)	(0.018)	(0.016)	(0.015)	(0.014)	(0.018)	(0.016)	(0.015)
Suppl. x Remaining Patent Days/1000	0.990	1.015	1.014	0.965	0.990	1.012	1.013	0.966
	(0.055)	(0.054)	(0.053)	(0.055)	(0.054)	(0.054)	(0.053)	(0.054)
Prevalence (Billions)	0.059	0.601	0.136	3.579				
	(0.237)	(2.932)	(0.629)	(15.666)				
Supplemental x Prevalence	102.715	235.653	32.724	1,056.946				
	(627.828)	(1,901.661)	(232.764)	(6,294.439)				
Mortality/100k					0.990	1.135	0.943	1.060
					(0.812)	(0.940)	(0.676)	(0.879)
Supplemental x Mortality/100k					0.898	1.081	1.080	0.965
					(0.455)	(0.414)	(0.493)	(0.387)
Observations	59,253	59,253	59,253	59,253	59,253	59,253	59,253	59,253
Generic Group Indicators		x				x		
Therapeutic Class Factors			x				x	
Mechanism of Action Factors				x				x
Model	Cox	Cox	Cox	Cox	Cox	Cox	Cox	Cox

Notes: Reported effects are hazard ratios. Other variables included but not reported are indicator variables for year, icd group, and missing prevalence/mortality data (with interactions). Standard errors clustered by icd group. Significance levels: *** p<0.01, ** p<0.05, * p<0.1.

After including additional control variables, Table 8 displays similar results as Table 7: the interaction effect *Supplemental* $\times$ *TRU* is not significantly different from one. The results for the control variables—with the notable exception of *Competition*—are similar to those in Table 4. Remaining days on patent has similar effects as previously: days remaining increases the hazard of approval for original uses. Relative to this effect, however, days remaining decreases the hazard of approval for supplemental uses, consistent with using supplemental approval as a way to maintain some exclusivity. This latter effect, however, is insignificant for France. Market size variables—including *Prevalence* and *Mortality*—are noisy and imprecise.

The results for France suggest no significant effect for the imposition of the TRU. As noted above, however, finding a true effect for France is complicated by the fact that it is a relatively small player in the global market. Moreover, with some approvals going through the European Union, changes in French policy may not create a large effect.

To assess whether this non-effect is a function of the above difficulties, we look for drug classes for which France may be a disproportionately large player. Since many of the drugs on the TRU were oncology drugs, we restrict Table 9 to cancer ICD codes only.[40] The results reported are similarly insignificant. Relatedly, and based on work discussing the importance of off-label uses for depression in France (Tunçel, 2023), we look at drug indications for psychoaffective disorders. The results in Table 10 show that *Supplemental* $\times$ *TRU* is still insignificant here as well. These extensions suggest that the roll-out of the policy–and the anticipated continuation of prescription patterns—muted any potential effect on pharmaceutical companies.

4.3 Discussion

The results in Section 4 are broadly consistent with firms responding to government incentives to submit uses for formal approval.

[40]For Tables 9 and 10, we cluster standard errors by drug id due to the small number of icd groups.

The consistent pattern reflected in these results is interesting in light of the difference in the nature of these policy changes. When weighing the relative merits of undergoing formal approval for an additional use of a drug, the ability to promote off-label uses of drugs is a significant benefit. In the United States, the policy change was limited to that of promotion. Where previously firms were not confident about marketing off-label uses of their drugs to physicians, *Caronia* changed this. After *Caronia*, the benefits of leaving a use off-label increased. Without the threat of criminal liability for promoting off-label uses, pharmaceutical companies have fewer costs associated with leaving uses off-label while still retraining the benefits of off-label sales. Consistent with this effect, we see evidence that the hazard of approval for supplemental uses, relative to original uses, in the US declined after *Caronia*. These effects are both statistically and practically significant across a variety of samples and specifications.

The TRU regulation is a more complicated change. While physicians were supposed to enroll their patients into TRU monitoring programs upon prescription, prior evidence suggests that this was not the case in practice. And while pharmaceutical companies were intended to be encouraged to apply for formal approval, the existence of the TRU period of monitoring could actually extend the time between Phase III and approval (rather than file for formal approval immediately, a firm may delay for the state-sanctioned three-year monitoring period). Accordingly, pharmaceutical companies could rationally expect unchanged or even increased benefits of leaving uses off-label under the TRU. In line with this strategic behavior, we are unable to detect a change in hazard of approval for supplemental uses in France after TRU implementation.

Of course, in terms of pure market size, France is a much smaller player than the United States. Indeed, France is a small player even within the context of the EU. Given the increasingly uniform approval process at the EU level, rather than at the nationwide level, the effect of French policy is more likely to be muted. However, even in drug classes for which France should be a bigger global player, the effects are statistically insignificant.

These results are consistent with firms prioritizing uses of their drugs to submit for formal approval in response to the restrictions (or freedoms) a country enacts toward off-label promotion and prescription. Liberalization of promotion–particularly in a large market–seems to be very influential, while weak enforcement of even stringent regulations may fall short.

Future work should incorporate information on cost of approval to examine a different margin: firm selection of indication to serve as the original approval. If off-label prescription is sufficiently costless, firms may prefer to keep only one use on-label. Selection of which indication to serve as the original approval would reflect the cost of approval,[41] the relative value from direct to consumer advertising (as opposed to physician promotion), and other such factors.

While these results have economically interesting implications about the type of regulations that may influence firm behavior, the significance of these results are also incredibly practical. While off-label use need not present a threat to the practice of medicine, formal approval serves an important function. Not only does its signal value decline if firms opt to keep more uses off-label for reasons unrelated to efficacy, but formal approval was a chief incentive for conducting costly—but extremely probative—scientific studies. If the incentive declines—particularly if it declines for specific indications—the informational landscape may significantly change in a way that would threaten patient care.

5 Conclusion

Off-label regulation has important ramifications for companies, physicians, and patients. Not only do off-label regulations affect the way that pharmaceutical companies strategically manage their research pipelines, but their behavior has important consequences for the amount of scientific information available to the public. The paper articulates a conceptual

[41] Some indications involve more costs to prove safety and effectiveness. This may be because the magnitude of the effects are so small that a larger sample is necessary to have sufficient power. Additionally, diseases which require a longer examination time frame would result in higher costs of testing.

model of firm strategy and presents results consistent with firms strategically responding to new regulatory changes. This paper sought to analyze periods in which countries undertook unprecedented off-label regulation. The United States liberalized its regulatory regime by reducing the legal cost associated with off-label promotion. With this newfound ability to promote off-label uses, firms should be marginally more likely to leave a drug use off-label rather than file for formal approval. Using data from firms' research and development pipelines, this paper finds that the hazard of formal approval declines for supplemental uses relative to original uses, consistent with firms leaving uses off-label to minimize costs. This result is robust to a number of specifications, inclusion of many control variables, and to within- and across-country analyses.

France took a more stringent policy stance—nominally restricting the prescription of off-label uses—but neglected to enforce it. Our analysis could find no significant effect of this regulatory change. While France is a smaller global player, which may account for some of the insensitivity, no significant effect is discernible even for drug classes that are particularly important in France. This result highlights the necessity of proper enforcement of even the most restrictive regulations.

While the results focus on firm behavior, their importance extends to the availability of quality data on drug efficacy . The perverse effects of the liberalization of off-label promotion can result in the decline of rigorous studies on new drug indications. In considering such a policy change, governments should consider the potential effects on patient welfare caused by the different informational landscape and the diluted signal value of formal approval.

References

Acemoglu, D., Linn, J., 2004. Market size in innovation: Theory and evidence from the pharmaceutical industry. Quarterly Journal of Economics 119, 1049–90.

Auffret, M., Rolland, B., Caous, A.S., Gaboriau, L., Deheul, S., Bordet, R., Gautier, S.,

2018. On-the-ground application of the 'temporary recommendation for use' regulatory measure on off-label use of baclofen for alcohol dependence in france: a regional survey of community pharmacies. Fundamental & clinical pharmacology 32, 234–238.

Cockburn, I.M., Lanjouw, J.O., Schankerman, M., 2016. Patents and the global diffusion of new drugs. American Economic Review 106, 136–64.

Covington, Burling, 2015. New french rules on off-label use. URL: https://www.natlawreview.com/article/new-french-rules-label-use.

Degrassat-Théas, A., Bocquet, F., Sinègre, M., Peigné, J., Paubel, P., 2015. The "temporary recommendations for use": A dual-purpose regulatory framework for off-label drug use in france. Health Policy 119, 1399–1405.

Drogou, F., Netboute, A., Giai, J., Dode, X., Darmon, D., Kassai, B., Letrilliart, L., 2019. Off-label drug prescriptions in french general practice: a cross-sectional study. BMJ open 9, e026076.

Dubois, P., De Mouzon, O., Scott-Morton, F., Seabright, P., 2015. Market size and pharmaceutical innovation. The RAND Journal of Economics 46, 844–871.

Emmerich, J., Dumarcet, N., Lorence, A., 2012. France's new framework for regulating off-label drug use. New England Journal of Medicine 367, 1279–1281.

Gentry, E.P., McMichael, B.J., 2020. Responses to liability immunization: Evidence from medical devices. Journal of Empirical Legal Studies 17, 789–819.

Liu, S., Mello, M.M., Kesselheim, A.S., 2021. Prospects for enforcing prohibitions on off-label drug promotion after united states v. caronia: An analysis of litigated cases. Journal of Health Politics, Policy and Law .

Philip, E., 2014. United states v. carolina: How true does truthful have to be. Vand. L. Rev. En Banc 67, 157.

Radley, D.C., Finkelstein, S.N., Stafford, R.S., 2006. Off-label prescribing among office-based physicians. Archives of internal medicine 166, 1021–1026.

Robertson, C., 2014. When truth cannot be presumed: The regulation of drug promotion under an expanding first amendment. BUL Rev. 94, 545.

Tunçel, T., 2023. Should we prevent off-label drug prescriptions? empirical evidence from france. Forthcoming at the Review of Economic Studies .

Yin, W., 2009. R&d policy, agency costs and innovation in personalized medicine. Journal of health economics 28, 950–962.

A Appendix Tables

Table 9: Proportional Hazard Model for Approval: TRU, Within-Country, Cancer Only

Variables	(1)	(2)	(3)	(4)
Supplemental	1.737	1.616	1.475	2.885*
	(1.073)	(1.220)	(0.931)	(1.821)
Supplemental x TRU	1.539	0.907	1.343	0.621
	(1.150)	(0.796)	(1.134)	(0.514)
Observations	18,707	18,707	18,707	18,707
Generic Group Indicators		x		
Therapeutic Class Factors			x	
Mechanism of Action Factors				x
Model	Cox	Cox	Cox	Cox

Notes: Reported effects are hazard ratios. Other variables included but not reported are indicator variables for year and icd group. Standard errors clustered by individual drug. Significance levels: *** p<0.01, ** p<0.05, * p<0.1.

Table 10: Proportional Hazard Model for Approval: TRU, Within-Country, Psychoaffective Disorders Only

Variables	(1)	(2)	(3)	(4)
Supplemental	2.897**	1.505	2.049	4.360***
	(1.459)	(0.779)	(1.227)	(2.178)
Supplemental x TRU	0.405	0.322	0.204	0.211
	(0.409)	(0.346)	(0.225)	(0.244)
Observations	2,323	2,323	2,323	2,323
Generic Group Indicators		x		
Therapeutic Class Factors			x	
Mechanism of Action Factors				x
Model	Cox	Cox	Cox	Cox

Notes: Reported effects are hazard ratios. Other variables included but not reported are indicator variables for year and icd group. Standard errors clustered by individual drug. Significance levels: *** p<0.01, ** p<0.05, * p<0.1.

B Data Construction Appendix

The following describes how the Citeline data is used to construct our data set. The data was downloaded in February 2019. Citeline provides data on the drug's phase of development in a given country, which we treat as comprehensive list (though not indication-specific). Citeline also provides data on the development status for all indications for which the drug was developed; however, it does not tell us what stage was reached in each country. Citeline also lists a history of drug developments. Finally, Citeline provides rich text blurbs describing the drug's Marketing (Approval/Launches), Phase I, Phase II, and Phase III stages.

Using this data, we create a drug-indication specific data set. For each original observation with n diseases associated with it, we create n observations.[42] For the purpose of this paper, we assume that pre-launch is a unitary process, undifferentiated by country. While each country has its own pre-launch process, if we consider the firm to be the aggregator of information about its drug's potential uses, information from a Phase I study in one country is likely to be informative for a Phase I study in another. Since we are concerned with when a firm discovers such information about this drug, we create global dates for Phase I, Phase II, and Phase III for each indication. Our analysis relies on approval dates, but we use the launch date to infer an approval date when approval dates are missing.

The best source of information is the Citeline text associated with Marketing (Approval/Launches), Phase I, Phase II, and Phase III. In order to scrape these dates, we use a number of sophisticated string analysis techniques. We also use information from the drug's event history, as this often lists dates when an indication changes phases or receives approval/is launched in a given country. Often, this information is not indication-specific. In order to ensure that we are not being too liberal with assigning dates, we take the following measure: we search the history for the first mention of the indication. If the indication is mentioned in the history, any history before the first mention is no longer considered. This

[42] After constructing the dates (and obtaining country-specific approval dates), we reshape the data such that each observation is a drug-indication-country observation.

ensures that previous approvals prior to the introduction of a new indication are not ex-post extended to the new indication. If the indication is never mentioned separately, we assume the entire history applies to the indication. We then record the earliest launch/approval date that mentions the relevant country. We also extract dates from the country-specific development field described above. This again is not indication-specific; before assigning a year in a country to an indication, we use the development history to determine whether the date extracted is attributable to the given indication.

After we have all these possible dates, we decide which dates to use. For approval dates, we prefer to use the text dates, as they are generally indication-specific. If that is not available, we use dates from the drug's development history. If that is not available, we use date from the country-specific development status.

For phase dates, we look at the minimum approval dates over all countries. Using this "Earliest Approval Date," we check the consistency of our Phase III dates. For Phase III, we also prefer to use dates from Citeline's text blurbs. We extract three types of dates: dates associated with press releases, Scrip dates, and Clinical Trial dates. The press release and Scrip dates are directly from the text, so the program pulls the earliest of each of these dates. For ClinicalTrials, the program pulls all relevant Clinical Trial numbers. It then searches for these trials on ClinicalTrial.gov and then chooses the latest completion date associated with the earliest start date. If a text date is missing (or is later than the Earliest Approval Date), we use dates from the drug's development history.[43]

We do a number of sanity checks on these dates, such as designating as missing dates preceding 1920 and after 2300 and approval dates that precede Phase III dates. For approval/launch dates, if Citeline lists the country as having only reached a stage prior to approval/launch, all approval/launch dates (for any indication in that country) were noted as nonexistent. Similarly, if the indication global status of the drug had not reached these

[43]In doing so, we look for evidence of a phase change and the relevant indication. If we find an entry indicating the correct phase change and indication, we note this as an indication-specific date. If we can only find a date with the correct phase date (but not indication, although occurring within the history attributable to the indication), we collect that date.

stages, all approval/launch dates associated with that indication are considered nonexistent. When approval dates are missing but launch dates are not, we impute approval dates as a year prior to launch. For phase dates, a similar process occurs.