WORKING PAPERS

N° 1459

January 2026

# "Strategic Submissions: An Analysis of Supplemental Drug Approvals"

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# Strategic Submissions: An Analysis of Supplemental Drug Approvals

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January 28, 2026

**Abstract**

Off-label use regulation has the potential to change pharmaceutical firms' behavior and—consequently—affect patient welfare. We investigate the impact of changes in off-label regulation on pharmaceutical firms' behavior in seeking formal marketing approval for supplemental 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. Using a unique data set of pharmaceutical firms' research and development projects, we exploit this regulatory change to understand how firms react to government policies. Results demonstrate that the hazard of approval declined for supplemental uses, relative to original uses, after the policy change. Patent protection, potential market size, and competition are also important determinants of the hazard of approval. These results have implications not only for innovation policy but for the creation of high-quality data for certain indications.

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

**JEL Codes**: I10, D22, L20, I18

# 1 Introduction

All developed countries require drugs to be approved for at least one use before the drug is marketed. Drug approval is not substance-specific: instead, regulatory agencies approve drugs only for the specific diseases (or "indications") requested by pharmaceutical companies. This sequential process of innovation and regulatory approval creates opportunities for firms to strategically exploit differences in policy to maximize sales and minimize regulatory costs. This paper examines the effect of an exogenous shock to the liability associated with forgoing formal supplemental approval on firms' willingness to leave a use "off-label." It finds evidence consistent with firms strategically choosing formal supplemental approval to exploit the newfound ability to promote off-label uses and to maximize market exclusivity.

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 (Wong et al., 2014), administrative procedure, and government incentives to innovate (Yin, 2009; Chandra et al., 2024)) and benefits of approval (e.g., expected market size (Acemoglu and Linn, 2004; Dubois et al., 2015), competition (Khmelnitskaya, 2023; Aghion et al., 2005), and price (Cockburn et al., 2016). The types of costs and benefits, however, differ based on whether the use is the first approval for the drug (an "original" use) or an additional use (a "supplemental" use).

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. Physicians are not constrained to prescribe on-label but instead are generally free to prescribe drugs for off-label uses. The continued access to the market constitutes a significant difference

for supplemental uses. 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. Consistent with prior literature (Tunçel, 2025; Radley et al., 2006), this paper will concentrate on the prescription of drugs for different indications.

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,[1] 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 (Radley et al., 2006; Tunçel, 2025; Berger et al., 2021). 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 (2025) 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 studies. Moreover, large-scale studies have better chances of identifying rarer safety risks. Such expensive studies are most likely to be undertaken by pharmaceutical companies in pursuit of formal approval. Given

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

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. Other off-label prescriptions could result from physicians relying 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 neither supports a treatment decision in the most robust way nor incentivizes creation of better public scientific information about a drug use.

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 process called "detailing" or "promotion." While most countries allow pharmaceutical companies to promote on-label uses, most restrict 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]

Against this backdrop, this paper focuses on a recent change in off-label drug use policy. In December 2012, the United States relaxed its restrictions on off-label promotion based on the theory that such promotion is protected by the First Amendment. After a federal Circuit Court ruling which extended 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. An additional analysis, located in the Appendix, focuses on a nominally more drastic change in off-label regulation in France.[4]

Using a unique data set listing the research and development projects for pharmaceutical firms, this paper exploits these regulatory changes 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

[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]Description of the regulatory change, methodology, and results are left to Appendix C.

approval in the US. These results are robust to a variety of specifications and to within- and across-country comparisons.

## 1.1 Related Literature

In examining the effect of a reduction in liability on firm incentives to submit a drug use for formal approval, this paper contributes to two strands of existing literature: incentives to innovate and the phenomenon of off-label uses.

It is well-documented that firms strategically respond to government incentives to bring products to market (Chandra et al. (2024); Grennan and Town (2020); Garthwaite et al. (2021); Gupta and Kao (2024)). 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. Other studies concentrate on the effects of explicit research subsidies or expedited pathways to obtain approval. Chandra et al. (2024) examine the effect of new approval pathways on the efficiency of the approval process and safety of the resulting approvals. They find that the Breakthrough Therapy Designation was able to shorten clinical development time while not increasing adverse events associated with the approved drugs. 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.

This paper contributes to a burgeoning literature which focuses on the effect of a perceived reduction in litigation liability on firm incentives to innovate. Such perverse reactions to new government regulation are 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 con-

sistent 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 changes in liability for off-label promotion on firm incentives to submit pharmaceuticals for formal approval.

In addition to tackling the decision to bring a drug to market, this paper focuses on decisions surrounding supplemental uses of a drug: e.g., the choice to leave a use off-label or to submit for formal approval. The decision to file for supplemental approval is slightly different than the decision to file for an original approval, since off-label prescription is generally legal. Prior literature has examined the effect of allowing for off-label prescription on health costs and outcomes. Tunçel (2025) estimates a structural model of physician treatment choice, allowing off-label uses to be a treatment choice and modeling supply as Nash-in-Nash bargaining between the government and pharmaceutical companies. Estimating the model on French prescription data, Tunçel estimates that banning off-label prescription leads to a 15% increase in prescription drug expenditures without any improvement on health outcomes. Related lines of literature have examined trends in approvals; in particular, DiMasi (2013) tracks the number of supplemental approvals from 1998-2011, differentiating between supplemental approvals seeking to add new indications (to both brand-name and generic drugs) and those expanding access to a pediatric population. This paper contributes to this strand of literature by examining an exogeneous change in liability that should affect the relative benefits of leaving a use off-label. While this paper cannot measure welfare effects of the resulting change in behavior, it tackles questions about the connection of broader policy changes to pharmaceutical behavior left by other papers (Tunçel, 2025).

## 1.2 Structure of the Paper

The paper proceeds as follows: Section 2 explains the regulatory background surrounding off-label use, the policy changes enacted during the study period, and the consequent effect on supplemental uses. Section 3 discusses the conceptual model and empirical strategy in

identifying the effects of the change in off-label regulation. Section 4 describes the data and presents descriptive statistics, and Section 5 presents evidence consistent with firms strategically responding to such policy incentives. Section 6 concludes.

# 2 Institutional Background

The exogenous change examined in this paper is the change in misbranding liability for off-label promotion. While the United States allows off-label prescription, it previously prohibited direct-to-physician promotion of off-label use by pharmaceutical companies. 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. Such off-label promotion was presumptively illegal under the Food, Drug, and Cosmetic Act (FDCA).[5] This interpretation continued, though years of First Amendment jurisprudence slowly chipped away at the foundations.

In 2012, however, a major court decision changed the expectations of liability for off-label promotion. In *United States v. Caronia*,[6] 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.[7] While the Second Circuit's decision was not formally binding on the entire country,[8] 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.[9] 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

[5]Title 21 United States Code §352.
[6]Decision of United States Court of Appeal, Second Circuit, Volume 703 Federal Reporter 3d 149 (2012).
[7]A more detailed history of the misbranding jurisprudence is provided in Appendix A.
[8]Circuit opinions are only binding within the Circuit.
[9]Amarin Pharma, Inc. v. U.S. Food & Drug Admin., 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015)

the facts (Liu et al., 2021).[10] 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.

Importantly, our policy change of interest is the liability for off-label promotion, not the effect of *Caronia* itself. The paper uses *Caronia* as a shift in the underlying liability, and insofar as pharmaceutical companies updated their beliefs of expected liability through related litigation, the results present an underestimate of the impact of the change in misbranding liability for off-label promotion overall.

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.

# 3 Conceptual Model and Empirical Strategy

## 3.1 Conceptual Model

As mentioned above, while off-label use refers to the prescription of drugs for any age, dosage, or indication for which it did not receive formal approval, this paper adds to the prior literature focusing on prescriptions for unapproved indications (Tunçel, 2025; Radley

[10]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).

et al., 2006). 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 to not sell a drug, firms decide between filing for approval for an additional indication or leaving the use off-label (while still selling the drug).[11] In order to continue making money on off-label uses, however, pharmaceutical companies must persuade physicians to prescribe their drug for off-label uses. To do this, firms generally engage in direct-to-physician promotion.[12] 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. A drug typically completes 4 stages before approval:[13] 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

[11] As noted above, while off-label refers to any prescription of a drug for an indication, dosage, or population for which it did not receive formal approval, this paper concentrates on the prescription for a different indication.

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

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

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, and is generally costlier than prior phases (Wong et al., 2014). During this stage, more information on safety and effectiveness is collected, along with information on dosages and interactions with other drugs. After completing Phase III, the pharmaceutical company will formally ask for approval.

Because we are interested in understanding a pharmaceutical company's decision to file for approval once it believes a use is viable, we use a hazard model to capture the temporal relationship between changing benefits of approval and the hazard of approval. In doing so, we want to compare the hazard of failure (approval) for original and supplemental uses during periods in which the temporal relationship to approval should be comparable prior to the regulatory change.

### 3.1.1 Choice of Origin Point

In modeling the decision to submit a drug for formal approval, we have to choose an origin point, i.e. a phase at which the observation becomes "at risk" of failure. We choose the beginning of Phase III as an origin point, such that companies have completed Phase I and Phase II and accordingly have general evidence of safety and effectiveness from those prior phases. This choice is ideal for two reasons.

First, at the beginning of Phase III, a company has some evidence of both safety and effectiveness that it can use to promote the drug off-label. Phase I provides evidence of drug safety and Phase II provides some evidence of efficacy (albeit in small samples). Only conditioning on initiating Phase I and II will include observations in which the company may not have results to promote even without approval. Phase III is a more expensive phase, so a company may rationally decide not to complete it and leave the use off-label using the data from prior phases as promotional material.

Second—and most importantly—the primary assumption of a difference-in-differences analysis is that the treated and untreated groups's trends would be comparable absent treatment. Since an original use is often the first to go through Phase I, there may be different factors affecting its hazard of completing that stage (which in turn, affects its hazard of formal approval). Similarly, insofar as less information is available for original uses than for supplemental uses (because supplemental uses have already had the drug approved for another use), this difference declines as phases progress. Put simply, the hazard of approval seems most comparable for original and supplemental uses after Phase I and Phase II due to extant evidence on safety and initial efficacy.

One concern about choosing Phase III as an origin point might be that companies face little additional cost to submit a drug for formal approval after reaching Phase III. We do not consider this a problem for two reasons. First, even if Phase III trials were completed, even the application fee for applications requiring clinical data is $4 million (and $2 million for applications not requiring clinical data) for FY 2025. While this is not the majority of drug development costs, it is also not trivial. Second, the median number of "pivotal" efficacy trials for each approved indication from 2005-2012 was 2 (Downing et al., 2014), meaning that even the completion of one Phase III study often does not mean that Phase III is over. Third, if the additional cost for approval is too small, this would bias against a significant finding. Similarly, insofar as a company decides to not even begin a Phase III trial and instead market the use off-label, our model estimates would provide a lower bound of the effect of legal reform.

In addition to the reasons noted above for why conditioning on Phase III best captures the decision between formal approval and off-label use, using the Phase III date as the origin point does not create selection effects. The difference-in-differences model captures the change in hazard of approval after *Caronia*. If companies already know whether they will keep a use off-label by the origin point (the beginning of Phase III), and their decision is not influenced by the new legal freedoms afforded by *Caronia*, our coefficient of interest

will be insignificant. While it is possible that a negative Phase III result might cause a firm not to file for formal approval, this is the same before and after *Caronia*. For this reason, using the Phase III date best isolates candidates for pharmaceutical choice while isolating any change in such choice created by the legal change.

### 3.1.2 Identifying Assumptions

Three important assumptions underlie our analysis.

**Assumption 1: Use of Approval.** First, we cannot reliably observe when drugs in our research and development sample are submitted for approval, only when they receive approval. We cannot supplement this research and development data with external data to obtain submission dates because the FDA has a policy of not acknowledging or disclosing data on submitted-but-not-approved drug applications. To accommodate this limitation, we use approval as our "failure"; 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.

**Assumption 2: Global Phase Dates.**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 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. We do think this is a more accurate description of the pharmaceutical companies' process, both due to the FDA's increased willingness to accept international data and the capacity of international data to promote an off-label use.

**Assumption 3: Original Uses as Controls.** Finally, 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[14] possible, it is empirically rare for our study. Violation of the control group assumption essentially means that any significant result is caused by the increase in hazard for original approvals, relative to supplemental approvals, rather than the relative decline of the latter. This concern can be separated into two related empirical phenomenon: first, that original approvals have a higher hazard of approval after *Caronia*, driving the relative reduction in hazard for supplemental approvals. The second margin is that during this period the composition of indications used as original approvals changed, as firms invest in original approvals that are cheaper to approve. As noted below in Section 4.6, we fail to find evidence of either mechanism.

[14]There are several theoretical reasons to predict that this would not be an empirically important margin. First, in such a case, the original use must itself be unprofitable, prior to the regulatory change. 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 on-label prescriptions plus pre-*Caronia* off-label prescriptions must be also unprofitable. Moreover, since none of the supplemental uses would have been submitted as original uses, each supplemental use must have been 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). Since our analysis condition on reaching Phase III, the relevant changes should happen at Phase III. 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.

## 3.2 Empirical Strategy

The paper uses survival analysis to estimate the differential effect of off-label regulation on the hazard of drug approval for a given indication. The hazard function estimates the likelihood of survival (remaining unapproved) at time t, conditional on an observation reaching time t without approval. It essentially allows for differences in the relationship between time and failure based on treatment, conditional on other control variables.

The analysis allows for an observation-specific origin point—the Phase III date—at which point the observation becomes "at risk." Drug indications are observed until either formal approval or until the end of the sample period (censored). Failure in this model is indicated when the observation is approved. The indication-specific origin ensures that the outcomes are not conflated with observation period (i.e., later observations are not incorrectly seen as having a lower hazard of approval). Instead, the hazard function at any given t *from the origin* is compared across observations, and time-varying covariates are allowed to change the hazard function. This captures our metric of interest much more specifically than simply estimating the likelihood of approval by treatment status.

As noted above, the model treats the pre-approval process as unitary across countries, allowing phase III trials in one country to place an observation "at risk" in other countries. As noted in Section 3.1.2, we choose Phase III as the origin for several reasons. Because Preclinical and Phase I involves collecting initial evidence of safety—and because the safety data from original uses can transfer to supplemental use—we wait until the use completes these stages. Phase II provides some evidence of efficacy, which creates materials that pharmaceutical representatives could use to promote the drug use off-label. Finally, original and supplemental use approval hazards are more similar at later stages, given the extant evidence on safety for supplemental uses. Given this established approval process, we condition on the date associated with Phase III status and estimate the hazard that the use is approved. By constructing the hazard model this way, we can assess the marginal impact of the policy

changes concerning off-label use/promotion on the hazard rate of supplemental approvals.

Our model requires time-varying treatment, which we obtain by splitting the data in two ways. 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 after the original approval. This definition of supplemental does not require perfect prediction of the first approval (i.e., the original use). All uses are constrained to have the same hazard ratio until the first approval, after which a separate ratio is estimated for supplemental uses.

The second time-varying treatment is by year. We split the survival time into year-long 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 allow us to designate *Caronia* as years 2013 onward.[15]

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

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

where the event is defined as approval of drug $d$ for indication $i$. $h(t)_{id}$ is the hazard that drug $d$ is approved for indication $i$ at time $t$. Any approval date that was subsequent to the end of the sample period was treated as not having been approved by the end of observation.

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

[15]The holding of *Caronia* was issued in December 2012.

where $Supplemental_{idt}$ is an indicator variable for whether the use of drug $d$ for indication $i$ in year $t$ is considered supplemental. As noted above, *Supplemental* is time-varying at the drug-indication level such that until the original approval of the drug for any indication, *Supplemental* is 0 for all indications of that drug. After the original approval, all other indications for drug $d$ are candidates for supplemental approval (*Supplemental*=1). *OLDU* is a generalization of the Off-Label Drug Use (OLDU) regulatory change, which represents *Caronia* in the US.[16] $Caronia_t$, reported in the results section below, is an indicator for whether $t$ is after the *Caronia* holding. 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 $t$. Prevalence of disease $i$ controls for the potential market size of such indication in the country, which is likely to positively affect approval. $X_t^d$ 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 $i$.[17] 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.

# 4 Data and Descriptive Statistics

## 4.1 Research and Development Data

The main source of data is from Citeline, Informa Pharma Intelligence.[18] 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

[16] *OLDU* represents TRU in France. See the appendix for details on the regulatory change in France and the results on this change. $TRU_t$ in the appendix is an indicator for whether $t$ falls after the TRU regime was passed.

[17] 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.

[18] This data was downloaded in February 2019.

status of each disease worldwide, and key events in the development process. Using a string-processing algorithm, we use the data to determine the dates of approval for each disease for a sample of countries.[19]

Using this data and algorithm, we construct a dataset in which a single observation is a unique drug-indication entry. Only observations with non-missing Phase III dates are retained.[20] We limit observations to those with Phase III dates between 2000 and the date of download (February 2019).[21]

The indications in the Citeline data, while detailed, require standardization. In order to operationalize this rich data, we crosswalk the indications listed in Citeline to ICD-10 codes.[22] In order to do so, we use a mixture of automated string matching and manual matching to match indications to ICD codes of varying specificity. We then group ICD-10 codes into 87 broader disease categories. This allows us to control for differences in hazard of approval by broad disease categories.

## 4.2 Drug Classification

In order to account for differences in hazard of approval by drug characteristics, we use 3 strategies. First, we create "generic group indicators" by grouping drugs 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[23] 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

[19] 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, is available upon request.

[20] 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.

[21] For France, we impute EU dates if they precede the national dates of approval.

[22] 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.

[23] Sometimes a drug is too preliminary to have a name or only has an alphanumeric name.

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.[24] This still leaves us with a large number of indicator variables.[25] 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 these approaches to control for differences in drug substance.

## 4.3 Competition Data

To control for potential competitors in a given indication, we use the Citeline data itself. Our measure of competition is the number of substances getting approval in the same ICD category and country 5 years prior. This is a much more detailed measure of competition than can be found outside of the data, as we observe development of specific ICD codes (rather than therapeutic classes, which do not always line up with indication). The country-specific measure seeks to capture the fact that certain markets might be saturated with recently-approved substances at different times. The 5 year lag allows for a forward-looking firm to anticipate waning exclusivity. In addition to the lag, we normalize the competition measure by subtracting the mean number of approved substances within each country and ICD category over the period studied. What remains is a measure of deviation from the mean number of competitors, such that we can interpret this measure as a reaction to relatively high levels of competition.[26] This data is merged into the Citeline data by year, country,

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

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

[26] This construction solves the ambiguous nature of competition noted in by removing the market size component of competition.

and ICD group.[27]

## 4.4 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; Berger et al., 2021). 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[28] 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.[29] While we would ideally prefer a more detailed measure of prevalence, the broad categories provide a measure of potential 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.[30]

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

[27]Previous versions of the analysis had used competition data from earlier stages of development. Namely, competition was measured by the number of substances each year that reaches Phase III in a given ICD category. Notably, this measure cannot be country-specific, glossing over different competitive pressures felt in each market. 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. The results related to competition using this measure were largely insignificant.

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

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

[30]We represent this value in billions for ease of coefficient interpretation.

sex. We use the death count for all ages and sexes for a country in a given year.[31] 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. We then aggregate deaths across the range of ICD codes associated with each indication.

## 4.5 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 date as the relevant filing date, we approximate the expiration date as twenty years after. For any given date interval in our data, we subtract the date from the expiration date, creating a "Remaining Patent Days" measure. We represent this value in terms of thousands for ease of coefficient interpretation. Once the patent expiration occurs, this value becomes zero (as does any observation with no patent associated with it).

While we would like to use data from Orange Book on other types of exclusivity, many of our observations never reach approval. Accordingly, data on patent rights for approved drugs (such as the Orange Book) would force us to exclude unapproved drugs. Data from the PAIR database allows us to keep not-yet-approved drugs.

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

## 4.6 Descriptive Statistics

Table 1 presents some basic descriptive statistics regarding approved drugs across countries and years, breaking out these averages by time periods, 2000-2012 and 2013-2018. Comparing the average supplemental approvals per drug across columns shows a drop in supplemental approvals for the United States and France. These data are simply suggestive, however. The following section displays results for the full models.

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

| | United States | | France | |
|---|---|---|---|---|
| | 2000-2012 | 2013-2018 | 2000-2012 | 2013-2018 |
| Total approvals | 1014 | 898 | 873 | 706 |
| Original approvals | 765 | 660 | 762 | 618 |
| Supplemental approvals | 249 | 238 | 111 | 88 |
| Supp. approvals per drug (ave.) | .49 | .47 | .27 | .24 |

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.

Figure 1 presents a histogram showing the percentage of original and supplemental indications that received approval within two, three, and five years after the start of Phase III trials. For the pre-*Caronia* period, the figure includes all observations with Phase III trials initiated before Caronia and for which the corresponding two-, three-, and five-year windows conclude prior to *Caronia*. It then reports the approval rates separately for original and supplemental indications. The same approach is applied to the post-*Caronia* period, including Phase III trials initiated after Caronia and allowing the respective approval windows to extend up to (and including) the end of the sample period.

Revisiting Assumption 3 from Section 3.1.2, a potential concern about using original approvals as a control group is that a change in off-label regulation may theoretically increase the hazard of approval for original uses. Figure 1 and Tables 2—3 demonstrate that this is not likely and that original uses serve as a good control group for this study. As noted

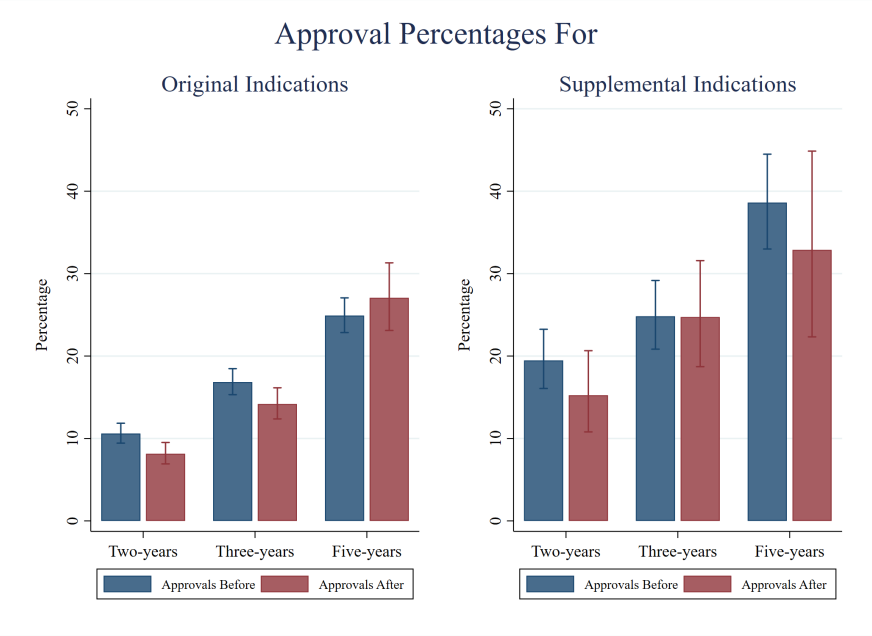


Figure 1

above, the two related concerns are that *Caronia* causes the hazard of approval to increase for original uses (and does not affect supplemental uses); we can see that this is not the case from Figure 1. Figure 1 shows a rightward shift in approval rates for original indications, with approval rates exhibiting a small decline in two-and three-year windows, followed by a slight increase in the five-year window following the start of Phase III trials.[32] For supplemental uses, approval rates decline for two of the three time horizons. This contradicts the concern that the results capture a change in original indications, not supplemental.

Relatedly, the concern about the composition of indications submitted as original approvals leading to a higher hazard of approval is not supported by Tables 2–3. Using the ClinicalTrials.gov database, we collect information on Phase III trial enrollment and duration (both intended to proxy the cost of trials) for each indication and group the data by

[32]For each indication-drug entry, we need to allow sufficient observation periods when calculating approval percentages, which means excluding many drug-indication entries for each time-horizon. For instance, for the five-year period, we exclude all indication-drug entries with a Phase III start date after 12/03/2007 and before *Caronia* because their five-year observation period overlaps with the *Caronia* date. Similarly, for the five-year horizon in the after-*Caronia* period, we exclude all drug-indication entries with a Phase III start date after 02/26/2014, because there is insufficient observation time for them until the end of the sample period. The exact numbers of excluded drug-indication entries are reported in the Table B4 in the appendix, separately for the before and after-*Caronia* periods and original and supplemental entries.

three-digit ICD codes. We assign each ICD group into quartiles of enrollment and duration. In Tables 2 and 3, we compare the number of original uses in each duration/enrollment quartile depending on whether the original approval was granted before or after *Caronia*. The tables (and associated chi-squared statistics) are below. Given the Pearson chi-square test for equality across proportions, we fail to reject the null hypothesis that the proportions are equal: the original uses approved pre- and post-*Caronia* do not have significantly different distributions across cost quartiles proxied by the enrollment size of the trial or the duration of the trial.

Table 2: Original Approvals in Each Duration Quartile

| Duration Quartile | Caronia =0 | Caronia = 1 |
|---|---|---|
| 1 | 155 | 184 |
| 2 | 120 | 108 |
| 3 | 127 | 148 |
| 4 | 112 | 111 |

Note: There are 1,238 uses approved with Phase III dates after 2000. Of these, we were able to match duration data to 1,065 observations (displayed in table). The chi-square statistic for equality across proportions is Pearson chi2(3) = 3.4392 Pr = 0.329.

Table 3: Original Approvals in Each Enrollment Quartile

| Enrollment Quartile | Caronia =0 | Caronia = 1 |
|---|---|---|
| 1 | 48 | 61 |
| 2 | 75 | 85 |
| 3 | 190 | 183 |
| 4 | 200 | 220 |

Note: There are 1,238 uses approved with Phase III dates after 2000. Of these, we were able to match enrollment data to 1,062 observations (displayed in table). The chi-square statistic for equality across proportions is Pearson chi2(3) = 2.0412 Pr = 0.564.

These descriptive statistics preview the results from the proportional hazard model de-

scribed below.

# 5 Results

In this section, we present the results of a proportional hazard model. Results of a weibull parametric model are displayed in the main text, and results from a cox proportional model are displayed in Appendix B. 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. 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.[33]

The difference-in-difference model follows equation (2). As noted above, we split the survival time into year-long 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 allow us to designate *Caronia* as years 2013 onward. Because we include a full set of year indicator variables, however, we do not report the main effects for *Caronia* in the following results, as it is not meaningful. Given that we split our units of observations, we can have multiple intervals of time for each drug-indication unit.[34]

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 4. The columns vary by the method by which we control for drug substance characteristics, indicated by the fourth, fifth, and sixth rows.

The interaction term $Caronia \times Supplemental$ is associated with a hazard ratio below

[33]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.

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

Table 4: Weibull Proportional Hazard Model for Approval: Caronia

| Variables | (1) | (2) | (3) | (4) | (5) |
|---|---|---|---|---|---|
| Supplemental | 5.607*** | 5.750*** | 6.172*** | 5.784*** | 6.685*** |
| | (1.056) | (1.074) | (1.216) | (1.059) | (1.312) |
| Supplemental x Caronia | 0.807 | 0.686** | 0.759 | 0.758 | 0.707* |
| | (0.144) | (0.111) | (0.141) | (0.137) | (0.132) |
| Observations | 53,612 | 53,612 | 53,612 | 53,612 | 53,612 |
| Generic Group Indicators | | x | | | |
| Therapeutic Class Factors | | | x | | x |
| Mechanism of Action Factors | | | | x | x |

**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.

one, indicating that the hazard rate of formal approval for supplemental uses declines in the post-*Caronia* period relative to the rate for original uses. This sparse specification produces estimates that are statistically significant at conventional levels when including generic group indicator variables (column 2) or both mechanism of action and therapeutic class factors (column 4). The estimated coefficients on $Caronia \times Supplemental$ imply a reduction of approximately 30% in this differential, with the magnitude ranging from 20% to 30% resulting from the hazard ratios of 0.807 in column (1) and 0.686 in column (2), respectively.

Table 5 presents the same models as Table 4, 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. We allow for the impact of competition with *Adjusted Competition* which is significantly less than 1 at the 10% level across all specifications. Across all specifications, this is consistent with firms strategically using formal approval when competition is expected to be lower.

Table 5: Weilbull Proportional Hazard Model for Approval: Caronia

| Variables | (1) | (2) | (3) | (4) | (5) |
|---|---|---|---|---|---|
| Supplemental | 9.091*** | 9.179*** | 10.509*** | 9.428*** | 11.573*** |
| | (2.176) | (2.345) | (2.749) | (2.280) | (3.127) |
| Supplemental x Caronia | 0.590*** | 0.486*** | 0.551*** | 0.547*** | 0.502*** |
| | (0.114) | (0.102) | (0.113) | (0.116) | (0.115) |
| Adjusted Competition | 0.972* | 0.972* | 0.971* | 0.972* | 0.972* |
| | (0.016) | (0.016) | (0.016) | (0.016) | (0.016) |
| Mortality/100k | 1.148 | 0.999 | 1.103 | 1.099 | 1.101 |
| | (0.293) | (0.201) | (0.237) | (0.260) | (0.246) |
| Supplemental x Mortality/100k | 1.268*** | 1.302*** | 1.258*** | 1.254*** | 1.258*** |
| | (0.089) | (0.131) | (0.091) | (0.096) | (0.092) |
| Remaining Patent Days/1000 | 1.171*** | 1.180*** | 1.189*** | 1.178*** | 1.194*** |
| | (0.017) | (0.019) | (0.017) | (0.018) | (0.019) |
| Suppl. x Remaining Patent Days/1000 | 0.808*** | 0.826*** | 0.801*** | 0.807*** | 0.796*** |
| | (0.036) | (0.051) | (0.037) | (0.039) | (0.040) |
| Expedited Review Designation | 2.439*** | 2.341*** | 2.391*** | 2.500*** | 2.336*** |
| | (0.292) | (0.261) | (0.275) | (0.286) | (0.260) |
| Orphan Drug Act Status | 1.222 | 1.009 | 1.259 | 1.195 | 1.232 |
| | (0.180) | (0.163) | (0.196) | (0.183) | (0.193) |
| Observations | 53,612 | 53,612 | 53,612 | 53,612 | 53,612 |
| Generic Group Indicators | | x | | | |
| Therapeutic Class Factors | | | x | | x |
| Mechanism of Action Factors | | | | x | x |

**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.

We also include indicator variables for whether a drug has received an expedited review or orphan drug designation. *Expedited Review Designation* is uniformly significantly greater than 1, consistent with theory. *Orphan Drug Act* 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.

*Remaining Patent Days* is significantly greater than one, suggesting a higher hazard of approval corresponding to more days remaining on-patent.[35] *Remaining Patent Days* $\times$ *Supplemental* is significantly less than one, suggesting that relative to original uses, remaining time reduces the proportional hazard of supplemental approval (or more intuitively, less time increases the proportional hazard of supplemental approval). This is consistent with firms strategically using supplemental formal approvals to retain some level of exclusivity. To further unpack this effect, Table 6 transforms *Remaining Patent Days* into 4 categorical variables: $No\ Remaining\ Patent\ Days$, $Remaining\ Patent\ (0-5\ Years)$, $Remaining\ Patent\ (5-10\ Years)$, and $Remaining\ Patent\ (>10\ Years)$ (omitted category). By estimating the effect of these categories and their interaction with *Supplemental* status, the story becomes clear. Relative to greater than ten years of patent protection (the omitted category), the hazard of approval for original uses declines for all shorter protection categories. This is consistent with firms filing for approval early in the patent life of a drug. Relative to this, however, supplemental status increases the hazard of filing for approval as remaining days get smaller. $No\ Remaining\ Patent\ Days \times Supplemental$ is significantly greater than one indicating that when patent life expires, the hazard of approval for supplemental uses multiplicatively significantly increases relative to original uses, consistent with using supplemental approval to extend exclusivity. $Remaining\ Patent\ (0-5yrs) \times$

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

Table 6: Weilbull Proportional Hazard Model for Approval: Caronia, Disaggregated Patent

| Variables | (1) | (2) | (3) | (4) | (5) |
|---|---|---|---|---|---|
| Supplemental | 2.684*** | 2.812*** | 2.864*** | 2.695*** | 2.951*** |
| | (0.522) | (0.640) | (0.580) | (0.508) | (0.591) |
| Supplemental x Caronia | 0.593*** | 0.490*** | 0.548*** | 0.547*** | 0.496*** |
| | (0.120) | (0.102) | (0.119) | (0.118) | (0.117) |
| Adjusted Competition | 0.970* | 0.971* | 0.969* | 0.969* | 0.970* |
| | (0.016) | (0.016) | (0.016) | (0.016) | (0.016) |
| Mortality/100k | 1.105 | 0.978 | 1.055 | 1.065 | 1.056 |
| | (0.263) | (0.195) | (0.221) | (0.233) | (0.228) |
| Supplemental x Mortality/100k | 1.259*** | 1.286** | 1.236** | 1.248*** | 1.243*** |
| | (0.101) | (0.140) | (0.102) | (0.107) | (0.104) |
| No Remain. Pat. Days | 0.349*** | 0.329*** | 0.319*** | 0.335*** | 0.309*** |
| | (0.033) | (0.033) | (0.031) | (0.031) | (0.032) |
| No Remain. Pat. Days x Suppl. | 4.279*** | 3.980*** | 4.817*** | 4.601*** | 5.278*** |
| | (0.966) | (1.214) | (1.122) | (1.091) | (1.308) |
| Remain. Pat. Days (0-5 Years) | 0.268*** | 0.278*** | 0.272*** | 0.272*** | 0.288*** |
| | (0.091) | (0.102) | (0.095) | (0.095) | (0.104) |
| Remain. Pat. Days (0-5 Years) x Suppl. | 1.798 | 1.960 | 1.894 | 1.766 | 1.863 |
| | (0.793) | (1.014) | (0.866) | (0.784) | (0.839) |
| Remain. Pat. Days (5-10 Years) | 0.470*** | 0.472*** | 0.480*** | 0.487*** | 0.499*** |
| | (0.097) | (0.117) | (0.097) | (0.105) | (0.106) |
| Remain. Pat. Days (5-10 Years) x Suppl. | 0.877 | 0.865 | 0.861 | 0.839 | 0.852 |
| | (0.279) | (0.298) | (0.263) | (0.264) | (0.258) |
| Expedited Review Designation | 2.371*** | 2.262*** | 2.362*** | 2.411*** | 2.285*** |
| | (0.295) | (0.264) | (0.281) | (0.291) | (0.268) |
| Orphan Drug Act Status | 1.185 | 0.999 | 1.220 | 1.174 | 1.204 |
| | (0.180) | (0.169) | (0.198) | (0.184) | (0.195) |
| Observations | 53,612 | 53,612 | 53,612 | 53,612 | 53,612 |
| Generic Group Indicators | | x | | | |
| Therapeutic Class Factors | | | x | | x |
| Mechanism of Action Factors | | | | x | x |

**Notes:** Reported effects are hazard ratios. The omitted category is remaining patent days exceeding 10 years. 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 7: Weibull Proportional Hazard Model for Approval: Caronia

| Variables | (1) | (2) | (3) | (4) | (5) |
|---|---|---|---|---|---|
| Supplemental | 10.665*** | 11.368*** | 12.428*** | 10.522*** | 12.913*** |
| | (3.628) | (4.103) | (4.498) | (3.552) | (4.678) |
| Supplemental x Caronia | 0.605*** | 0.503*** | 0.562*** | 0.553*** | 0.505*** |
| | (0.114) | (0.105) | (0.112) | (0.114) | (0.112) |
| Adjusted Competition | 0.972* | 0.972* | 0.971* | 0.972* | 0.972* |
| | (0.016) | (0.016) | (0.016) | (0.016) | (0.016) |
| Prevalence (Billions) | 3.893 | 1.847 | 5.495 | 7.880** | 8.857 |
| | (3.889) | (2.769) | (7.702) | (7.580) | (11.978) |
| Supplemental x Prevalence | 0.095 | 0.042 | 0.067 | 0.200 | 0.160 |
| | (0.195) | (0.104) | (0.156) | (0.367) | (0.326) |
| Remaining Patent Days/1000 | 1.171*** | 1.178*** | 1.188*** | 1.178*** | 1.193*** |
| | (0.017) | (0.019) | (0.017) | (0.018) | (0.019) |
| Suppl. x Remaining Patent Days/1000 | 0.807*** | 0.818*** | 0.802*** | 0.806*** | 0.796*** |
| | (0.035) | (0.051) | (0.037) | (0.039) | (0.040) |
| Expedited Review Designation | 2.499*** | 2.424*** | 2.447*** | 2.561*** | 2.393*** |
| | (0.294) | (0.257) | (0.270) | (0.287) | (0.255) |
| Orphan Drug Act Status | 1.191 | 0.968 | 1.234 | 1.175 | 1.217 |
| | (0.179) | (0.159) | (0.197) | (0.186) | (0.198) |
| Observations | 53,612 | 53,612 | 53,612 | 53,612 | 53,612 |
| Generic Group Indicators | | x | | | |
| Therapeutic Class Factors | | | x | | x |
| Mechanism of Action Factors | | | | x | x |

**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.

*Supplemental* is greater than one, though never statistically significant.

Table 7 performs the same analysis as Table 5, 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 5.

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

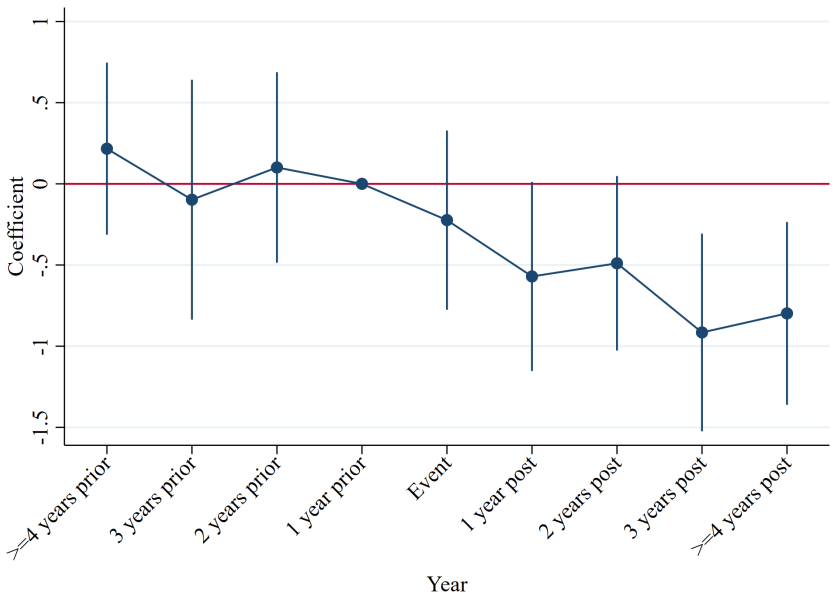


Figure 2: Event Study: Caronia

**Notes:** The coefficients plotted in the figure follow the specification in Table 5, 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.

baseline period. Figure 2 plots the coefficients[36] 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 expect with an exogenous shock, the effects for the event and subsequent periods are negative and significant.

## 5.1 Discussion

The results presented in Section 5 reflect the lower incentives to submit supplemental uses for formal approval created by a reduction in misbranding liability. Where previously firms were not confident about marketing off-label uses of their drugs to physicians, *Caronia* changed this and increased the benefits of leaving a use off-label. Without the threat of criminal liability for promoting off-label uses, pharmaceutical companies have fewer costs

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

associated with leaving uses off-label while still retaining the benefits of off-label sales. Consistent with this change in misbranding liability, we see evidence that the hazard of approval for supplemental uses, relative to that of original uses, declined after *Caronia*. These effects are both statistically and practically significant across a variety of samples and specifications. As noted above, the paper does not attempt to examine the effect of *Caronia* but rather the effect of the reduction in off-label promotion liability. Based on the evolution of the commercial free speech doctrine to *Caronia*, our results may represent an overestimation of the effect of *Caronia* itself; however, they are an underestimate of the effect of the reduction in liability for off-label promotion.

While this paper does not examine the welfare effects of such a change—and indeed, the prevalence of off-label prescriptions can benefit patients (Viscusi and Zeckhauser, 2015)—the results have practical implications for patient care. While off-label use need not present a threat to the practice of medicine, formal approval serves an important function. Not only does the signal value of formal approval 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. The chief cost of reducing liability for off-label promotion, accordingly, is an informational one.

The potential effects for patient care is that a high level of uncertainty over off-label treatments' efficacy might persist. While uncertain treatments can create potential benefits for patients, creation of generalizable efficacy data is difficult outside the context of randomized controlled trials. Unless manufacturers (or research labs) have reason to undertake the cost of sufficiently powered randomized trials, patients must impute efficacy on a more individual basis.

Finally, the results add to the body of literature emphasizing the importance of the downstream effects of potential markets on firms' strategic decisions. The increased ability

to promote off-label uses has direct effects on the potential sales of a drug, creating lower incentives to pursue formal approval. This is especially interesting in light of the additional analysis in Appendix C, which examine the consequences of a purportedly more stringent restriction on off-label use in France. The regulation in France was meant to restrict the off-label uses of drugs, requiring pharmaceutical companies to track prescriptions and collect safety data. Despite this, the results do not reflect any significant effect on pharmaceutical companies' actions in submitting uses for formal approval. Other work on the French off-label regulation change suggest that physicians did not change their prescription behavior in light of the new regime, interpreting the restrictions as applying only to pharmaceutical companies. If pharmaceutical companies anticipated no change in prescription behavior, the strong rhetoric and symbolic regulation likely would not affect firm behavior. In setting policy, the government should be specifically sensitive to changes that plausibly affect drug sales.

# 6 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 model of firm strategy and presents results consistent with firms strategically responding to new regulatory changes.

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 evidence of this: 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 and to inclusion of many control variables.

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.

# 7 Funding

This work was supported by the Agence Nationale de la Recherche under grant ANR-17-EURE-0010 (Investissements d'Avenir program), funding from the TSE-P Health Center whose lists of sponsors can be found at https://www.tse-fr.eu/health, and the public funding under the "PSPC" call for projects operated on behalf of the French government by Bpifrance as part of the "investments for the future" program (PIA) ARPEGE. Funding sources had no role in study design, collection, analysis and interpretation of data, writing of the report, or decision to submit the article for publication.

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# A Appendix: Description of Legal Changes

This section provides more detail about the legal landscape of off-label regulation and addresses potential policy confounders.

While the FDA had long maintained that off-label promotion by manufacturers is misbranding in violation of the Federal Food, Drug, and Cosmetic Act,[37] changes in the commercial free speech doctrine had whittled away the FDA's legal grounds (Philip, 2014; Robertson, 2014). In the late 1990s and early 2000s, the FDA tried to promulgate guidance about how pharmaceutical companies could distribute information about off-label uses. A court held that the nature of this guidance violated the commercial free speech doctrine, so the FDA reframed the requirements as a safe harbor (such that firms complying with the restrictions would not be found liable for misbranding). In 2002, the Supreme Court held that the FDA's restrictions on compounding pharmacies' promotion of drugs also violated commercial free speech.[38] In 2011, the Supreme Court held that restricting the sale of prescriber-identifying information was also unconstitutional. After these decisions, the Second Circuit's decision in *Caronia* most directly addressed the truthful of off-label promotion.[39] As noted above, however, the paper focuses not on the effect of *Caronia* but on the effect of the change in liability for off-label promotion. The results presented are an underestimate of the latter, given the developments in commercial free speech doctrine.

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 that are false or fraudulent for reimbursement to the government. For off-label promotion, FCA claims allege that pharmaceutical companies fraudulently cause a claim for

[37] 21 U.S.C. 352.

[38] Compounding pharmacies are allowed to create customized versions of drugs to accommodate allergies or special dosages/form without FDA approval.

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

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.

Finally, 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 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.[40] In 2016, Congress passed The Medical Cures Act, which broadened the type of evidence that could be submitted as part of a drug application.[41] 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)."[42] Insofar as real-world evidence reduces the cost of approval, this could make filing for formal approval

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

[41] 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.

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

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*.

# B Appendix: Additional Tables

Table B1: Cox Proportional Hazard Model for Approval: Caronia

| Variables | (1) | (2) | (3) | (4) | (5) |
|---|---|---|---|---|---|
| Supplemental | 5.351*** | 5.374*** | 5.923*** | 5.451*** | 6.297*** |
| | (1.000) | (1.034) | (1.160) | (1.004) | (1.242) |
| Supplemental x Caronia | 0.894 | 0.732* | 0.831 | 0.840 | 0.767 |
| | (0.169) | (0.133) | (0.161) | (0.165) | (0.154) |
| Observations | 53,612 | 53,612 | 53,612 | 53,612 | 53,612 |
| Generic Group Indicators | | x | | | |
| Therapeutic Class Factors | | | x | | x |
| Mechanism of Action Factors | | | | x | x |

**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.

Table B2: Cox Proportional Hazard Model for Approval: Caronia

| Variables | (1) | (2) | (3) | (4) | (5) |
|---|---|---|---|---|---|
| Supplemental | 8.332*** | 8.514*** | 9.665*** | 8.684*** | 10.603*** |
| | (1.935) | (2.142) | (2.431) | (2.021) | (2.754) |
| Supplemental x Caronia | 0.663** | 0.520*** | 0.612** | 0.609** | 0.549** |
| | (0.135) | (0.115) | (0.130) | (0.134) | (0.130) |
| Adjusted Competition | 0.970* | 0.972* | 0.970* | 0.971* | 0.971* |
| | (0.017) | (0.016) | (0.016) | (0.017) | (0.017) |
| Mortality/100k | 1.101 | 0.969 | 1.060 | 1.061 | 1.055 |
| | (0.215) | (0.162) | (0.188) | (0.198) | (0.198) |
| Supplemental x Mortality/100k | 1.339*** | 1.332*** | 1.316*** | 1.331*** | 1.321*** |
| | (0.109) | (0.135) | (0.112) | (0.119) | (0.116) |
| Remaining Patent Days/1000 | 1.163*** | 1.175*** | 1.180*** | 1.170*** | 1.186*** |
| | (0.016) | (0.019) | (0.017) | (0.018) | (0.019) |
| Suppl. x Remaining Patent Days/1000 | 0.821*** | 0.828*** | 0.813*** | 0.816*** | 0.805*** |
| | (0.033) | (0.048) | (0.034) | (0.036) | (0.038) |
| Expedited Review Designation | 2.119*** | 2.041*** | 2.083*** | 2.186*** | 2.057*** |
| | (0.247) | (0.230) | (0.235) | (0.248) | (0.228) |
| Orphan Drug Act Status | 1.162 | 0.973 | 1.213 | 1.130 | 1.182 |
| | (0.169) | (0.157) | (0.188) | (0.172) | (0.182) |
| Observations | 53,612 | 53,612 | 53,612 | 53,612 | 53,612 |
| Generic Group Indicators | | x | | | |
| Therapeutic Class Factors | | | x | | x |
| Mechanism of Action Factors | | | | x | x |

**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 B3: Cox Proportional Hazard Model for Approval: Caronia

| Variables | (1) | (2) | (3) | (4) | (5) |
|---|---|---|---|---|---|
| Supplemental | 9.735*** | 10.391*** | 11.166*** | 9.633*** | 11.579*** |
| | (3.186) | (3.629) | (3.890) | (3.104) | (4.020) |
| Supplemental x Caronia | 0.689* | 0.547*** | 0.630** | 0.623** | 0.556** |
| | (0.137) | (0.121) | (0.131) | (0.133) | (0.127) |
| Adjusted Competition | 0.970* | 0.972* | 0.970* | 0.971* | 0.971* |
| | (0.017) | (0.016) | (0.016) | (0.017) | (0.017) |
| Prevalence (Billions) | 3.432 | 1.598 | 3.914 | 6.701** | 6.392 |
| | (3.219) | (2.198) | (5.329) | (6.050) | (8.314) |
| Supplemental x Prevalence | 0.095 | 0.047 | 0.091 | 0.211 | 0.216 |
| | (0.195) | (0.113) | (0.216) | (0.387) | (0.447) |
| Remaining Patent Days/1000 | 1.162*** | 1.173*** | 1.179*** | 1.170*** | 1.185*** |
| | (0.017) | (0.019) | (0.017) | (0.018) | (0.019) |
| Suppl. x Remaining Patent Days/1000 | 0.821*** | 0.822*** | 0.816*** | 0.816*** | 0.807*** |
| | (0.032) | (0.048) | (0.034) | (0.035) | (0.038) |
| Expedited Review Designation | 2.162*** | 2.106*** | 2.127*** | 2.232*** | 2.103*** |
| | (0.251) | (0.231) | (0.234) | (0.252) | (0.227) |
| Orphan Drug Act Status | 1.135 | 0.936 | 1.191 | 1.112 | 1.169 |
| | (0.168) | (0.153) | (0.188) | (0.174) | (0.186) |
| Observations | 53,612 | 53,612 | 53,612 | 53,612 | 53,612 |
| Generic Group Indicators | | x | | | |
| Therapeutic Class Factors | | | x | | x |
| Mechanism of Action Factors | | | | x | x |

**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.

Table B4: Number of Dropped Drug–Indication Observations in Figure 1

| | **Time Horizon (Years)** | | | | | |
|---|---|---|---|---|---|---|
| | **Before Caronia** | | | **After Caronia** | | |
| | Two | Three | Five | Two | Three | Five |
| Original Indications | 838 | 1194 | 1748 | 919 | 1338 | 2226 |
| Supplemental Indications | 106 | 164 | 309 | 48 | 85 | 198 |

*Notes:* The table reports the number of drug–indication observations excluded due to insufficient observation periods when calculating approval percentages. Exclusions are determined separately for each time horizon and for the periods before and after *Caronia*.

# C Appendix: French Policy

## C.1 Changes in French Policy

France has experienced its own change in policy regarding off-label prescription in the 2010s. 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 strengthening the safety of medicines and health care products. Together with a related decree regarding "Temporary Recommendations for Use" (TRUs), the law aims to provide a regulatory process for temporarily supervising the prescription of drugs for off-label indications (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 and to collect scientific information to ensure their safe use. Pharmaceutical companies bore the responsibility to track prescriptions of their drugs with a TRU and report any unusual prescriptions to the National Agency of Medicine and Health Product Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé [ANSM]) and take all appropriate measures to inform health care professionals and prevent off-label use (Emmerich et al., 2012).

The issuance of a TRU depended on the inherent safety of the drug, quality of existing scientific information, and the severity of the illness. The ANSM authorized a TRU if there were no other appropriate medications available (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 prescriptions (Emmerich et al., 2012). 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" (Rémuzat et al., 2013).

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),[43] 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 pharmaceu-

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

tical sales. This exercise presents a first pass at estimating sensitivities over the full sample of drugs.

## C.2 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.[44] 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 until approval, as the delay is essentially sanctioned by the French government.

Tables C1-C2 only examine behavior within France. Table C1 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.

After including additional control variables, Table C2 displays similar results as Table C1: the interaction effect $Supplemental \times TRU$ is not significantly different from one. The results for the control variables are similar to those in Table 7. 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. The effect of $Prevalence$ and $Mortality$ and their interactiosn with supplemental status are similar as the US's analysis, suggesting that similar determinants were significant for the hazard of approval. The effect of the TRU, however, is never statistically significant.

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

Table C1: Cox Proportional Hazard Model for Approval: TRU

| Variables | (1) | (2) | (3) | (4) |
|---|---|---|---|---|
| Supplemental | 2.620*** | 2.650*** | 2.599*** | 2.697*** |
| | (0.543) | (0.561) | (0.527) | (0.574) |
| Supplemental x TRU | 1.114 | 0.744 | 0.979 | 0.999 |
| | (0.225) | (0.178) | (0.206) | (0.224) |
| Observations | 55,364 | 55,364 | 55,364 | 55,364 |
| Generic Group Indicators | | x | | |
| Therapeutic Class Factors | | | x | |
| Mechanism of Action Factors | | | | x |

**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.

Table C2: Cox Proportional Hazard Model for Approval: TRU

| Variables_x | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) |
|---|---|---|---|---|---|---|---|---|
| Supplemental | 2.664*** | 2.374*** | 2.584*** | 2.672*** | 2.625*** | 2.264*** | 2.586*** | 2.564*** |
| | (0.533) | (0.470) | (0.546) | (0.561) | (0.650) | (0.531) | (0.592) | (0.649) |
| Supplemental x TRU | 1.074 | 0.783 | 0.977 | 0.977 | 1.064 | 0.758 | 0.962 | 0.957 |
| | (0.209) | (0.177) | (0.194) | (0.212) | (0.209) | (0.175) | (0.196) | (0.208) |
| Adjusted Competition | 0.939** | 0.941** | 0.938** | 0.938** | 0.939** | 0.941** | 0.938** | 0.938** |
| | (0.024) | (0.023) | (0.024) | (0.024) | (0.024) | (0.023) | (0.024) | (0.024) |
| Mortality/100k | 0.843 | 0.604 | 0.720 | 0.845 | | | | |
| | (0.700) | (0.533) | (0.533) | (0.694) | | | | |
| Supplemental x Mortality/100k | 4.432*** | 4.177*** | 5.133*** | 3.813*** | | | | |
| | (1.494) | (0.902) | (1.550) | (1.148) | | | | |
| Prevalence (Billions) | | | | | 0.173 | 30.215 | 0.461 | 2.743 |
| | | | | | (0.871) | (140.506) | (2.518) | (13.215) |
| Supplemental x Prevalence | | | | | 147.521 | 3,404.410 | 110.383 | 804.027 |
| | | | | | (1,220.999) | (21,486.383) | (826.591) | (6,111.205) |
| Remaining Patent Days/1000 | 1.064*** | 1.067*** | 1.072*** | 1.079*** | 1.065*** | 1.067*** | 1.072*** | 1.080*** |
| | (0.014) | (0.016) | (0.017) | (0.015) | (0.014) | (0.016) | (0.017) | (0.015) |
| Suppl. x Remaining Patent Days/1000 | 0.957 | 1.001 | 0.965 | 0.964 | 0.955 | 1.002 | 0.963 | 0.963 |
| | (0.045) | (0.052) | (0.050) | (0.052) | (0.046) | (0.052) | (0.051) | (0.053) |
| Observations | 55,364 | 55,364 | 55,364 | 55,364 | 55,364 | 55,364 | 55,364 | 55,364 |
| Generic Group Indicators | | x | | | | x | | |
| Therapeutic Class Factors | | | x | | | | x | |
| Mechanism of Action Factors | | | | x | | | | x |

**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.

## C.3 Discussion

The TRU regulation is a complicated change: purportedly very restrictive but with limited downstream effects. 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.

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. 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.[45]

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 importance of downstream prescription patterns to the efficacy of even the most restrictive regulations on pharmaceutical manufacturers.

[45] In analyses available upon request, we look at only observations associated with ICD codes corresponding to cancer or depression, as these are significant areas of treatment in France. Using these subsamples—and clustering errors by drug rather than ICD group due to the few included ICD groups—we largely find no significant result.