Drug Adoption under Uncertain Quality and Impact of FDA (De)Certification for Pediatric Patients*

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Abstract

We examine the adoption of untested drugs and how physicians' prescribing decisions respond to trials conducted in the pediatric population after initial market entry. While pediatric approval at market entry increases market share relative to no approval, physicians adopt drugs even in settings without corresponding FDA labeling information. Even though physicians use ex-post ineffective or unsafe drugs, the ex-post effective drugs comprise the majority of FDA-unapproved uses, indicating concordance between physician prescribing and FDA decisions. Subsequent FDA certification or decertification of pediatric uses of drugs have small impacts on prescription behavior due to high rates of off-label use and large delays between market entry and subsequent labeling changes.

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1 Introduction

A classic question in regulating product entry is the tradeoff between product quality and delays in valuable products entering the market due to regulatory compliance (Peltzman, 1973). While regulatory review ensures quality standards are met and lower quality products are screened out, it is also costly and time-consuming, which can prevent high-quality products from becoming available to consumers earlier. This question occurs in many industries where certification is needed for market entry, such as cars and airplanes (NHTSA, 2023; Code of Federal Regulations, 2023). These tradeoffs are most salient in the case of pharmaceuticals. Regulatory approval by the Food and Drug Administration (FDA) for new drugs might mean delayed access to life-saving drugs or drugs that improve quality of life. On the other hand, lax regulatory requirements may allow unsafe, ineffective, or otherwise harmful drugs to enter the market and be sold to consumers.

This paper sheds light on the benefits and harms of drug adoption under uncertain quality by: (a) examining the adoption of new drugs in cases with and without FDA approval, (b) evaluating the accuracy of physician prescribing decisions relative to subsequent FDA decisions based on clinical trials, and (c) estimating impacts of FDA certification and decertification on prescribing controlling for market learning. We focus on pediatric (aged 0-17) drug prescribing for two reasons. First, under the 1999 Pediatric Research Equity Act (PREA), drug sponsors applying for new drug approval must conduct pediatric assessments of pharmacokinetics, pharmacodynamics, safety, and efficacy for every new drug. While these requirements are often deferred or delayed, completion is mandatory, which allows us to observe FDA decisions for different drugs, diseases, and ages. Second, unlike in other pharmaceutical settings where reporting of negative clinical trial findings might be low or biased (Zarin et al., 2019; Oostrom, 2022), results from unsuccessful pediatric clinical trials must be reported to the FDA in order to comply with PREA requirements and are typically added to the drug label. Additionally, physicians are allowed to prescribe drugs off-label, defined as use of drugs in settings other than those indicated by the FDA, with limited legal liability or restrictions by pharmacies. The existence of relatively unrestricted off-label use allows us to observe prescribing patterns in the absence of FDA (de)certification and assess whether it aligns with subsequent FDA decisions.

We collect and combine data from Drugs@FDA, which is a publicly available database maintained by the FDA containing all drug label modifications by drug and date, with data from MicroMedex, one of the statutorily named medical compendia used by Centers for Medicaid and Medicare Services to create a historical record for each new drug approved between 1998-2013. This record contains all diseases and age ranges per disease that a drug was approved for, including dates of approval for each drug-disease-age combination. We call such approval dates "FDA certification events". We further supplement this data with information from the FDA's Pediatric Labeling Changes database which contains drug label changes associated with negative clinical trial results by drug-disease-age. We define "FDA decertification events" as drug labeling changes associated with lack

of efficacy or safety-related negative results such as finding more or different adverse events relative to adults, contraindications, labeling changes advising against use in pediatric patients, long-term adverse events, or insufficient data for establishing safety.

To measure prescribing for FDA-approved vs. FDA-unapproved uses, we use the Truven MarketScan Commercial Claims and Encounters data from 1996-2013. This data includes health insurance claims for active employees and dependents (including children) for a sample of employer-sponsored plans. Drug claims in MarketScan do not include information on what uses each drug was prescribed for; thus, we define FDA-approved uses of a drug for a given disease as those for which: (i) the patient associated with the drug claim was diagnosed with the disease prior to receiving the drug and (ii) the drug is FDA-approved for treatment of the disease and for the patient's age at the time of the drug claim. We classify all other uses as FDA-unapproved. Since physicians can prescribe drugs for conditions never approved by the FDA, we limit the patient sample to those diagnosed with diseases the drug was indicated for at the time of market entry. This allows us to examine prescribing and rates of FDA-approved and unapproved uses as a function of age rather than disease area.

In our final drug sample of 440 drugs approved between 1999-2013, only 29% of drugs were approved for some pediatric age at market entry. Because of such low pediatric labeling events at market entry, 1 in every 5 pediatric drug claims in our data are for an FDA-unapproved use. Frequently used off-label drugs in children (aged 0-11) include drugs used to treat asthma, skin and respiratory infections, as well as depression and anxiety drugs. 4 out of the top 10 most frequently prescribed off-label drugs among adolescents (aged 12-17) are used to treat mental health conditions, particularly depression and anxiety. Furthermore, up to 10% of drugs record a negative trial result for some pediatric age range. Addition of both negative and positive trial results to the drug label can be significantly delayed – conditional on FDA (de)certification at some point after initial market entry, the median drug is on the market for 8 years prior to the drug labeling change. Additionally, the average decertification event occurs 1.5 years later than the average certification event, suggesting that potentially harmful uses of a drug take longer to be labeled.

To examine drug adoption rates in the absence of FDA communication about safety and efficacy, we use an event study specification estimated around market entry of new drugs, specifically distinguishing between FDA-approved and FDA-unapproved uses. We find that patient and physicians adopt drugs even in the absence of FDA support (or lack thereof) for its use. Adoption of FDA-unapproved uses is fastest in the first year since market entry and remains constant and statistically significantly positive for up to three years after market entry; there is no de-adoption of FDA-unapproved uses. We also find that FDA-approved uses for pediatric age ranges at market entry are prescribed at twice the rate of unapproved uses. Drug adoption rates for both approved and unapproved uses are highest among treatment naive patients.

These results highlight one side of the tradeoff from regulatory inaction – untested and uncertified

products are certainly adopted by patients and physicians. This is not necessarily welfare-reducing, as this could mean that untested but effective and safe drugs are adopted. To examine whether physicians' prescribing decisions are in concordance with subsequent FDA decisions, we estimate an event study specification at initial market entry separately by ex-post outcome documented for the drug in clinical trials, grouping drugs into three categories: ex-post effective, ex-post unsafe or ineffective, and drugs never tested. Though imprecisely estimated, we find that most unapproved uses of drugs are for drugs that are ex-post shown to be safe and effective. However, ex-post unsafe or ineffective drugs are also adopted at a statistically significant positive rate. We find no evidence of de-adoption of these drugs up to three years after initial approval and prior to subsequent FDA decertification. Assuming that the FDA decision is in alignment with a social planner's decision, higher rates of adoption of untested but ex-post unsafe or ineffective drugs would indicate deviations from the social optimum. However, we find that even though prescribing rates for ex-post effective drugs are similar for more and less severe patients (as measured by prior emergency room and hospital utilization), ex-post unsafe/ineffective drugs are prescribed to more severe patients at higher rates. This may suggest that physicians are willing to try drug treatments that may not work for the average clinical trial patient but may work for more severe patients.

Under assumptions of Bayesian physicians with a mean-variance utility acting as perfect agents for their patients (McKibbin, 2020), subsequent FDA (de)certification events may not impact prescribing decisions if market learning already results in very precise physician beliefs prior to subsequent FDA labeling changes and physicians' beliefs are in concordance with the FDA's decision. To examine the empirical effects of subsequent FDA labeling changes on prescribing behavior, we separately estimate an event study specification estimating the impact of positive and negative FDA labeling changes on the probability of new drug claims. We find that subsequent FDA approval decisions increase prescriptions, though imprecisely estimated. FDA decertification events have no impact on prescribing. Given the median time of 8 years between market entry and subsequent labeling changes, our results are consistent with a model where long time periods of off-label prescribing and physician concordance with FDA decisions meaningfully reduces uncertainty around efficacy and safety so that subsequent FDA decisions have smaller impacts on prescribing relative to market learning.[1]

The paper proceeds as follows. Section 2 describes the regulatory setting and institutional background for drug approvals and pediatric prescribing. Section 3 outlines the empirical framework and event study specifications we estimate. Section 4 describes our data in detail and Section 5 shows summary statistics. Section 6 contains our main findings and Section 7 concludes.

[1] Our findings are consistent with recent findings estimating the effect of secondary FDA approvals for new diseases prescribing behavior (McKibbin, 2020; Berger et al., 2021). Ody and Schmitt (2019) also estimates the impact of subsequent positive and negative labeling changes for pediatrics and find similar though precisely estimated results due to the inclusion of all drug claims in the analysis rather than just those pertaining to the disease subject to the labeling change and thus may incorporate spillovers of FDA (de)certification across disease areas.

2 Setting and institutional background

2.1 Initial drug approvals and market entry

Regulatory agencies play a crucial role in ensuring that pharmaceutical drugs are safe and effective for use by patients. In the U.S., the Food and Drug Administration (FDA) is responsible for reviewing evidence submitted by drug sponsors to assess the drug's safety and efficacy (Burrows, 2006). Similarly, in the European Union, the European Medicines Agency (EMA) ensures that only safe and effective drugs are approved for use in the pharmaceutical drugs market (EMA, 2023). When reviewing evidence, regulatory agencies consider various factors, including dosage, pharmacokinetics, pharmacodynamics, safety, and efficacy submitted by drug sponsors for approval to enter the pharmaceutical drug market. For the remainder of the paper we will focus on the FDA as the regulator since our data comes from the U.S.[2]

Comprehensive data on various drug quality dimensions comes from clinical trials, which are often randomized, controlled, double-blind studies aimed at assessing the drug's safety and efficacy relative to a placebo or standard of care. As Pease et al. (2017) discuss, the FDA's usual requirement for approval includes more than one well-controlled clinical trial, but some of the clinical trial criteria for drug approval can be relaxed depending on the condition for which the treatment is under investigation, the standard of care, or the population size available for clinical trial enrollment (e.g., in the case for rare diseases).[3] The cost of conducting a clinical trial is entirely borne by the drug sponsor, which often is a pharmaceutical company and the drug patent holder.[4] The cost of a clinical trial can vary widely, depending on factors such as the complexity of the trial design, number of sites, the number of participants, and the duration of the trial (Moore et al., 2020).

The FDA reviews the submitted evidence on the drug's safety and efficacy and decides whether to approve the drug for market entry. Upon approval, several regulatory features begin. First, the drug sponsor can enter the pharmaceutical drug market and sell the drug to patients, subject to post-marketing surveillance, typically for adverse events (Alomar et al., 2020). Second, a 5-year market exclusivity period begins for the drug, which implies that only the drug sponsor is allowed to enter the market with the newly approved drug. The market exclusivity period may overlap with the drug patent period, but may also extend beyond the patent protection; it guarantees monopoly pricing to the drug sponsor (Kesselheim et al., 2017). Third, the FDA and the drug sponsor determine the indicated use of a drug, also called an indication (discussed in detail below).

[2] The regulatory setting in the European Union (EU) is quite similar as in the U.S. For a detailed comparison of the drug approval processes between the U.S. and EU, see Van Norman (2016).

[3] Recent trends suggest that these criteria are often relaxed to ensure faster market entry. For instance, between 2005-2012, over a third of drugs were approved based on a single pivotal trial and 44% were approved based on trials using surrogate endpoints instead of primary endpoints (Downing et al., 2014). Recent studies also show that the FDA Breakthrough Therapy designation has enabled faster market entry by simplifying clinical trial criteria for particularly valuable new drugs seeking approval (Chandra et al., 2022).

[4] Oostrom (2022) documents that half of treatment arms for psychiatric clinical trials can be considered as sponsored by industry.

Lastly, the drug sponsor can begin advertising the drug to patients and physicians for indicated uses only. Compliance with direct-to-consumer and physician advertizing regulations is also under FDA's purview (Li and Gibbs, 2021).

2.2 Drug indications

A drug's indication is a comprehensive description of all use cases of the drug for which the FDA has granted approval. The indication usually corresponds to the population in which the drug was tested in clinical trials.[5] Indications intend to highlight what uses are sanctioned by the FDA and act as salient, concrete, and easily accessible guidance for practitioners on cases in which the drug can be safely and effectively used. To achieve this goal, the indications are generally included at the start of the drug label and at the start of the drug's package insert. Historically, drug labels have not included approved age ranges because most drugs have traditionally been first approved for adults and the pediatric population has generally been underrepresented in clinical trials (Bourgeois et al., 2014). However, after the Best Pharmaceuticals for Children Act (BPCA) in 2002 and the Pediatric Research Equity Act (PREA) in 1999, pediatric indications have taken off.[6] All drug labels are publicly available in a database easily searchable by drug name called Drugs@FDA (discussed in more detail in Section 4.1), which ensures access to accurate and up-to-date information for all patients and practitioners.

As an example of an indication, Figure 1 shows the indications section of the drug label for Lexapro (escitalopram), one of the most frequently used antidepressants in the U.S. As Figure 1 shows, modern-day indications list the disease area and the ages for which a drug is indicated. For example, Lexapro is indicated for use for acute and maintenance treatment of major depressive disorder in adults and adolescents aged 12-17 years, as well as generalized anxiety disorder, but only in adults.

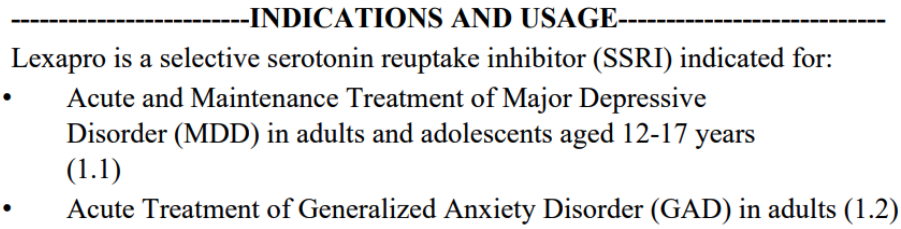
2.3 Secondary approvals and indications

Drug sponsors may investigate additional indications beyond those granted at market entry. For instance, they may study and seek approval for a new disease area, patients with a specific treatment history, or a new age group. Each additional approved indication earns the drug sponsor 3 years of market exclusivity. However, investigations of a drug's safety and efficacy for an already-approved disease but new pediatric age ranges earn the drug sponsor *at most* 6 months of additional market exclusivity, regardless of the outcome of the clinical trials conducted (i.e., regardless of whether the drug deemed safe and/or effective for children). Under BPCA, a drug sponsor can earn 6 months of market exclusivity if the FDA issues a written request for the drug sponsor to conduct pediatric

[5] Clinical trials have extensive lists of exclusion and inclusion criteria that patients must meet in order to participate in the study, usually specified in a pre-analysis plan. The indication may be more encompassing than these criteria and typically corresponds to the average patient enrolled in the trial.

[6] For more details on the regulatory background for pediatric indications, see Ristovska (2020) and FDA's Pediatric Report to Congress on BPCA and PREA.

Figure 1: Example indication section of a drug label



Note. This figure shows the indications section included at the beginning of the drug label for Lexapro. The full drug label for Lexapro is available here.

assessments and the drug sponsor completes the studies outlined in the written request.[7] In addition to these incentives, since 1999 drug sponsors are required to complete a pediatric assessment *for every drug* at the time of market entry, compliance with which offers no market exclusivity rewards. However, this requirement can be deferred or delayed, with drug sponsors frequently citing difficult recruitment as one of the reasons for deferral (Hwang et al., 2019, 2018).[8] Approximately 80% of all completed pediatric studies reported to the FDA are completed under PREA and not BPCA, indicating that compliance with the PREA requirements is a stronger incentive than the additional market exclusivity rewards provided under BPCA (FDA, 2020).

Additionally, any pediatric clinical trials that do not lead to pediatric approval must be reported to the FDA in order to comply with the requirements to conduct pediatric assessments under PREA. What is unique about secondary approvals in pediatrics is that results from unsuccessful pediatric clinical trials are added to the drug label as soon as they are reported to the FDA. While drug sponsors have been required to report trial results (positive or negative) for *any* indication to clinicaltrials.gov within 12 months of trial completion since 2017, only 66% of clinical trials complied with this requirement (Zarin et al., 2019). Furthermore, reported results, particularly from industry sponsors, are biased towards finding safe and effective uses of drugs, suggesting that negative trials in settings other than pediatrics (Oostrom, 2022). Thus, reporting of positive and negative pediatric trials provides an attractive setting to examine the impact of FDA certification and decertification of drugs since compliance with reporting negative results is higher in this setting and potential bias in reporting may be eliminated.

2.4 Off-label use

A unique feature of the pharmaceutical market is that physicians are allowed to prescribe drugs off-label, defined as use of drugs in settings other than those indicated by the FDA. Despite the

[7] The FDA issues written requests for drugs if it deems they will have "significant health benefits" in the pediatric population (FDA, 2022).

[8] This requirement is waived in cases where the disease rarely occurs in pediatric patients (Akalu et al., 2021).

potential risks associated with off-label use, physicians have only small legal liability with off-label prescribing, often solely in cases of serious adverse events (Syed et al., 2021). Additionally, when dispensing drugs, pharmacies often do not know what disease the drug was prescribed for by the physicians and thus rarely restrict drug access based on whether the use is consistent with the FDA indication. Despite no restrictions on physician and pharmacy discretion to use or fill drugs used off-label, additional restrictions may be introduced by insurers. For instance, insurers may require physicians to obtain prior authorization from the insurer to use new or expensive drugs by submitting forms detailing the use of the drug to the insurer. Such prior authorization forms often ask the condition for which the drug is used and in theory are designed to screen out medically unacceptable uses of a drug (such as off-label uses without an accepted evidence base) as well as reduce spending (Brot-Goldberg et al., 2023).

3 Empirical framework and estimation

3.1 Event study at initial market entry

Unlike in other product markets, the existence of off-label use in the market for pharmaceuticals allows us to directly observe whether there exists market learning and its speed in the absence of regulatory certification. Specifically, since off-label use is generally unrestricted for physicians and measurable in the data, we can observe adoption of drugs in the absence of any FDA communication (certification or decertification) on efficacy and safety for a subset of drugs that are not approved for some or all pediatric age ranges at initial market entry. We can also compare such prescribing patterns to rates of use for pediatric age ranges where the FDA has granted approval at market entry.

To assess the extent of drug adoption with and without FDA certification, we estimate the following event study specifications around the time of market entry of a newly approved drug among pediatric patients who have ever been diagnosed with any of the approved diseases at market entry:

$$onlab_{ijdt} = \gamma_{jd}^{on} + \nu_t^{on} + \sum_{k=-6}^{12} \beta_k^{on} \mathbb{1}(t - E_j = k) + x_{ijt} + \varepsilon_{ijdt} \tag{1}$$

$$offlab_{ijdt} = \gamma_{jd}^{off} + \nu_t^{off} + \sum_{k=-6}^{12} \beta_k^{off} \mathbb{1}(t - E_j = k) + x_{ijt} + \varepsilon_{ijdt} \tag{2}$$

where i denotes a patient, j denotes drugs, d denotes diseases approved for drug j at market entry, t represents calendar quarters, and E_j denotes the market entry date of drug j.[9] $onlab_{ijdt}$ and $offlab_{ijdt}$ denote our measures of drug demand with and without FDA certification – $onlab_{ijdat}$ refers to whether patient i diagnosed with disease d was prescribed drug j at time t consistent with the drug label at time t, whereas $offlab_{ijdt}$ refers to receipt of FDA-unapproved uses of drug

[9] While we refer to j as a drug, newly approved drugs may belong to multiple therapeutic drug classes, which is also included as an identifier but suppressed in the notation for clarity.

j at time t for patient i diagnosed with disease d. We estimate these models separately for on-label vs. off-label uses since diagnosed patients may receive no pharmaceutical drug treatment and we want to normalize our estimates relative to a denominator (diagnosed patient pool). γ_{jd} denote drug-disease fixed effects and ν_t denote calendar time fixed effects. x_{ijt} include the following controls for patient i's characteristics at time t: age by sex fixed effects, whether the patient has been treated with a drug in the same class as drug j prior to time t, which classifies patients into treatment naive and treatment experienced, whether the patient has had any emergency room (ER) or hospital visits in the 12 months prior to t, and fixed effects for the plan type the patient was enrolled in at time t.[10] As discussed in Section 2.4, different insurers may have different policies regarding permitting uses of drugs that are not FDA approved; thus controlling for insurance plans is crucial. The majority of patients in our data do not have plan identifiers, so we only control for plan type, which is populated for the vast majority of patients.

The estimated β_k^{off} coefficients capture whether physicians and patients adopt off-label drug uses (for which no FDA information is provided at market entry), whereas β_k^{on} capture the adoption of FDA-approved uses. These coefficients are identified using variation in the market entry time across drugs. To estimate the models in Equation 1 and Equation 2, we only use quarters before any subsequent information from the FDA is available for the drug, which isolates the effect of the initial information provided in the drug label at market entry. β_{-1} is normalized to zero at the quarter before market entry; since periods prior to E_j have no drug claims because the drug is not yet on the market, the pre-trends for this specification and any other specification around market entry of a drug will mechanically be zero.[11]

We make strides in assessing whether drug adoption under uncertain quality is valuable by re-estimating Equation (2) for drugs and ages with subsequent FDA certification/decertification events where the β_k coefficients are interacted with the outcome of subsequent pediatric assessments:

$$offlab_{ijdt} = \gamma_{jd}^{off} + \nu_t^{off} + \sum_{k=-6}^{12} \beta_k^{off} \mathbb{1}(t - E_j = k) * expost_{jda} + x_{ijt} + \varepsilon_{ijdt} \tag{3}$$

where $expost_{jda}$ denotes one of the following three categories: whether the drug j was ex-post approved for use in age a and disease d, ex-post not approved (due to lack of safety or efficacy) but tested in age a and disease d, or never tested for use in age a and disease d. The β_k^{off} coefficients estimated separately for each of these categories will thus identify drug adoption at market entry for drugs that are ex-post determined to be safe and effective versus those shown ex-post to be ineffective or have higher rates of adverse events.[12] We use certification and decertification events

[10] Plan types include basic/major medical, comprehensive, exclusive provider organization, health maintenance organization, non-capitated point-of-service, preferred provider organization, capitated or partially-capitated point-of-service, consumer-driven health plan, and high deductible health plan.

[11] Empirically, because of measurement error due to manually matching drug names to drug codes and since drug codes can be reused by drug sponsors/manufacturers for a new drug if prior drugs identified by the same drug code are discontinued, we are able to estimate non-zero pre-trends.

[12] Since there are no subsequent certification or decertification events for already approved uses of a drug, all drug

beyond the time period of our data to classify drugs based on-expost outcomes. Higher rates of adoption of ex-post effective drugs indicates that patients and physicians are good at choosing effective and safe drugs in the absence of FDA certification; higher rates of adoption of ex-post ineffective or unsafe drugs indicates that in the absence of FDA (de)certification physicians may choose suboptimal drugs.

3.2 Event study at subsequent FDA (de)certification events

We also examine the extent to which subsequent FDA certification events i.e., approvals expand the drug's market size in the approved age and disease group as well using a similar event study approach as in Equation (1) and Equation (1):

$$rx_{ijdt} = \gamma_{jd} + \nu_t + \sum_{k=-6}^{12} \beta_k \mathbb{1}(t - A_{jdt} = k) + timeonmkt_j + x_{ijt} + \varepsilon_{ijdt} \tag{4}$$

where A_{jda} denotes the FDA approval date for drug j, disease d, and age a. In addition to patient characteristics x_{ijt}, we also control for the time drug j has been on the market, denoted by $timeonmkt_j$. This intends to proxy as a control for the extent of market learning due to off-label use prior to the drug's subsequent approval. Unlike Equation 3, which uses data on certification and decertification events to classify drugs into ex-post outcome categories, we only use certification events that occur during the span of our data. We also estimate as similar event study model for additions of negative clinical trial results to the drug label, i.e., decertification events in order to capture potential decreases in the drug's market share:

$$rx_{ijdt} = \gamma_{jd} + \nu_t + \sum_{k=-6}^{12} \beta_k \mathbb{1}(t - D_{jdt} = k) + timeonmkt_j + x_{ijt} + \varepsilon_{ijdt} \tag{5}$$

where D_{jda} denotes the date the negative clinical trial result for drug j, disease d, and age a was added to the drug label.

Under assumptions of Bayesian physicians who update rationally in response to market learning and FDA communications about drug safety and efficacy, as well as under assumptions of physicians with a mean-variance utility function acting as perfect agents for their patients, FDA certification events should increase prescribing since they reduce uncertainty even if physicians are correct about drug efficacy (McKibbin, 2020). On the other hand, FDA decertification events also reduce uncertainty, but may decrease prescribing if physicians do not have accurate beliefs over drug efficacy. In such a model, if market learning already results in very precise physician beliefs prior to subsequent FDA approvals or labeling changes, additional FDA communications about drug safety and efficacy will have a negligible impact on prescribing if physicians have beliefs about drug safety and efficacy consistent with the FDA's decision.

claims with ex-post clinical trial outcomes are off-label.

4 Data and definitions

4.1 Sample drugs

We obtain a list of all drugs receiving their initial FDA approval for any age range and indication between 1998 and 2013 from Drugs@FDA, which is a publicly available database maintained by the FDA containing all FDA approvals, drug label modifications, and other FDA submissions by drug and date. We limit the sample to drugs in the 1998-2013 period because: (i) new indications and pediatric approvals were reliably recorded and time stamped starting in 1998, and (ii) 2013 is the end of the insurance claims data used to measure pharmaceutical demand (discussed below). Since drug names are not consistent across FDA submissions, we create a crosswalk between the 690 drug names gaining FDA approval and 661 unique active ingredients. 62 active ingredients were excluded because the active ingredient was approved before 1998.[13] 14 drugs were excluded because they were permitted to be used over the counter at some point during our data, which makes it difficult to measure demand in our data. We will henceforth use the terms "active ingredients" and "drugs" interchangeably, even though there can be multiple drugs with separate indications and clinical trials for the same active ingredient.[14]

4.2 Approved ages and indications

Each active ingredient was mapped to all indications and ages approved for use by the FDA as of March 2023 using the MicroMedex database, which is one of the statutorily named medical compendia by Centers for Medicaid and Medicare Services (CMS). We include all indications approved for an active ingredient, regardless of whether they were approved for a specific formulation, route of administration, dosage, or drug.[15] 11 active ingredients in our sample did not have indication information available, but the remaining 574 active ingredients were mapped to 958 indications. Among these indications, 30 were excluded because they were used to assist in diagnostic or imaging procedures, 42 were procedure-related (e.g., for post-operative or pre-operative care), and 78 were prophylactic, all of which cannot be reliably identified in the data. The final sample contains 511 active ingredients mapped to 781 indications.

MicroMedex does not list the dates of FDA approval for different ages and diseases. However, Drugs@FDA provides a historical record of changes to the drug label, including changes in the indication. Following Berger et al. (2021), we manually review these records for our sample drugs to determine ages approved for different diseases in the indication and dates of approval for each disease and age pair. This allows us to observe what ages and diseases were approved for a drug

[13] Entries in the Drugs@FDA database are often manually entered by drug sponsors or FDA staff. If drug names differ across FDA submissions for the same active ingredient, it is possible to observe a drug name first approved in 1998 or after even though the same active ingredient was entered under a different drug name prior to 1998.

[14] For example, depending on whether the drug is administered orally or intravenously, it might have a different drug name and clinical trials despite having the same active ingredient.

[15] This implies that we will not be able to identify dosage-based, formulation-based, and route-based off-label use in our data, leading to an underestimate of the actual off-label use.

at market entry versus what diseases and age groups are added to the indication at a later point.

Indications can be quite detailed (e.g., whether to use in treatment-naive vs. experienced patients, specific disease sub-types etc.). Such specificity of indications are not easily identifiable in our data, so we map indications to coarser disease categories that ignore the patient's treatment experience, disease sub-types and other similar details of the indication and can plausibly be mapped to ICD-9-CM diagnosis codes that are used to identify diseases in the data discussed below.[16] We define 310 such diseases among 781 indications.[17]

4.3 Tested ages and indications

Information on pediatric events triggering a drug label change for drugs approved between 1998-2013 comes from FDA's Pediatric Labeling Changes database.[18] In addition to approvals, this database contains a list of negative results for any pediatric populations, such as: finding more or different adverse events than adults, occurrence of serious side effects or contraindicated/not recommended uses in any pediatric populations due to serious side effects or long-term adverse effects, insufficient data for establishing safety, and efficacy not demonstrated in clinical trials.

We define events associated with ineffective drugs as those where efficacy was not demonstrated in clinical trials.[19] Events associated with unsafe drugs include those where the reported clinical trials found more or different adverse events relative to adults, contraindications, labeling changes advising against use in pediatric populations, additions of serious long-term adverse events, and insufficient data for establishing safety. For the purposes of this paper we exclude any events related to changes in dosing regimen or pediatric formulation release, which excludes 27 events and 14 drugs, because dosage information is typically bundled with safety/efficacy trials and is more difficult to determine changes in prescribed dosages in the data since dosages can more easily be adjusted outside of observable health care settings (e.g., taking half a pill or half an injection if a smaller dosage is recommended).

4.4 Drug claims

We use Truven MarketScan Commercial Claims and Encounters data from 1996-2013 to determine drug claims for sample drugs. This data contains all health insurance claims for active employees

[16] This method of mapping drugs to indications and dates of approval closely follows methods used by Berger et al. (2021).

[17] Since multiple indications can be mapped to the same disease, and approved age ranges across indications may differ, we take the widest possible age range as approved for each disease (across indications). This biases us towards considering more drug uses as on-label and away from considering them off-label, leading to an underestimate of off-label use.

[18] This database contains any positive or negative labeling changes for any drugs on the market since 1998-present, not only for newly approved drugs. However, since our estimation strategies use variation across drugs, we use the same sample of drugs first approved between 1998-2013 for estimating the impact of FDA labeling changes at initial approval vs. at times after initial market entry.

[19] If efficacy was demonstrated at some subsequent point in time for the same disease, we do not consider the event as negative.

and dependents while insured through a sample of employer-sponsored plans. The data encompasses a large set of enrollees – historically, the data has included 500+ million claims a year from approximately 100 plans. Importantly, it includes health insurance claims of any dependents of employees, which typically include children of employees. Patient age is included on all insurance claims in the data. We observe all emergency room visits, inpatient stays, outpatient visits, and pharmacy claims for enrollees in the data.

Drugs were identified in the prescription drug claims and medical claims. Prescription drug claims include drugs obtained at pharmacies whereas medical claims include drugs administered by a physician or in an inpatient setting (e.g., cancer drugs, biosimilars, and other injectables). Each active ingredient in our data was manually mapped to National Drug Codes (NDCs) used to identify pharmacy claims for sample drugs.[20] HCPCS codes were used to identify drugs in the medical claims, which were also similarly manually mapped to active ingredients. Unique drug claims were identified by unique patient ID, NDC code, refill number, date prescription was filled, days' supply, and quantity, whereas unique physician/hospital administered drugs were identified by patient ID, HCPCS code, quantity, and date drug was administered.[21] A small subset of sample drugs was excluded because there were no NDC/HCPCS codes identifying them or because there were zero drug claims for those drugs in the data. To estimate demand for drugs, we use all drug claims for sample drugs filled by pediatric patients, defined as aged younger than 18, yielding a sample of 25.8 million drug claims among pediatric patients between 1996-2013.

4.5 Defining FDA-approved and unapproved (off-label) uses

The drug claims in MarketScan do not include information on what uses each drug was prescribed for. Thus, on-label vs. off-label uses cannot be directly identified just based on the drug claim. To identify uses for which a drug might be prescribed, we use diagnosis codes reported in inpatient admissions, outpatient claims, facility claims, and inpatient services for each patient with a drug claim for a drug in our sample. To ensure that we have enough information on each patient to determine potential uses for a drug claim, we only classify drug claims as on-label or off-label where the patient had at least 12 months of medical data prior to the prescription.[22] Lastly, we only consider drug claims occurring after the patient was diagnosed with the indicated condition at market entry.

We additionally limit our sample of patients and drug claims for patients diagnosed with the initial disease that a drug was approved for. Because drugs can be used to treat diseases not approved by the FDA, this criterion ensures that we examine the impact of FDA decisions on age-based off-label use rather than disease-based off-label use. In other words, we only examine off-label uses for already-approved diseases but in ages without FDA approval.

[20] To minimize measurement error, NDC codes need to be recorded in the RedBook drugs database on or after the initial approval year for each drug.

[21] We cannot observe drugs that were prescribed but never filled by the patient.

[22] This medical enrollment periods need not be continuous.

For a drug claim to be classified as FDA-approved, it must satisfy the following criteria: (i) the patient associated with the drug claim must have been diagnosed with the indicated disease prior to the date associated with the drug claim, and (ii) the drug must be FDA-approved for treatment of the indicated disease for the patient's age at the time the prescription was filled or administered. This implies that drug uses not approved by the FDA but observable in the data include: (i) drug claims to ages never approved by the FDA and (ii) drug claims to ages not FDA-approved at the time of the drug claim, but approved at a later point.

5 Summary statistics

5.1 FDA certification and decertification rates across drugs

Our final drug sample contains 440 unique drugs and 852 approved drug-disease combinations, of which 624 were approved at market entry. Almost all indicated drug-disease combinations at initial market entry are approved for the adult population at the time of entry, defined as 18 years of age or older.[23] However, only 29% (180/624) of drug-disease combinations are approved for some subset of the pediatric population at market entry. An additional 132 drugs (21%) are approved for at least some at some point after entering the market without any pediatric approval and 10% of drugs have a negative labeling change for some pediatric age range.

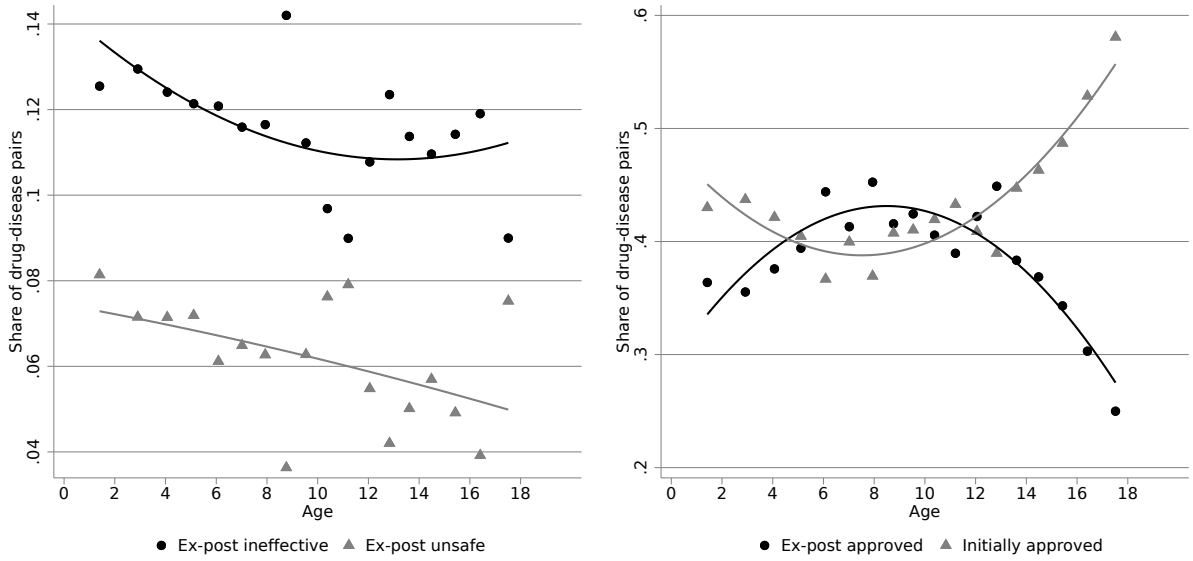
Figure 2 shows the probability of initial approval, subsequent approval (certification), subsequent decertification associated with drug inefficacy, and subsequent decertification associated with adverse events as a function of pediatric age. All figures control for disease fixed effects and thus compare the drug certification and decertification probabilities within diseases but across drugs.

The left sub-figure in Figure 2 shows that the highest rate of recording an ineffective result occurs between ages 2-6, and the probability of having a decertification event associated with drug inefficacy decreases with age. This sub-figure also shows that conditional on disease area, 5-8% of newly approved drugs are found to be unsafe in some pediatric age at some point after market entry; the share of drugs with decertification events associated with drug safety also decreases linearly with age.

The right sub-figure in Figure 2 shows that conditional on disease area, 50-60% of drugs are initially approved in some pediatric age and 40-60% are approved at some point after market entry. Since FDA approval is generally a terminal state, there is a negative relationship between initial FDA approval and subsequent FDA approval. The probability of initial approval increases with age, corroborating patterns in our collected data showing that expansions of indications to pediatric age ranges typically first target adolescent ages (12-17), and subsequent indications examine safety and efficacy in younger ages. The non-linearities associated with the probability of initial approval

[23] A small share of drugs, especially for those with high pediatric disease burden, were initially approved for the pediatric population only.

Figure 2: Probability of positive and negative events by age across drug-disease combinations



Note. The left sub-figure plots the share of drug-disease pairs having a finding of inefficacy or lack of safety after initial market entry as a function of pediatric age. The right sub-figure plots the share of drug-disease pairs with FDA approval at initial market entry and share of drug-disease pairs with FDA approval at some point after initial market entry. The sample includes all new drugs approved by the FDA between 1998-2013 and includes all initial indications that were FDA-approved. Both figures include disease fixed effects. Data on indications and ages associated with certification and decertification events comes from MicroMedex database, Drugs@FDA, and FDA's Pediatric Labeling Changes database.

as a function of age may be due to measurement error – when collecting the data on approved ages, we assume that a drug is approved for ages 0-18 if pediatric approval is mentioned but age ranges are not specifically mentioned.[24]

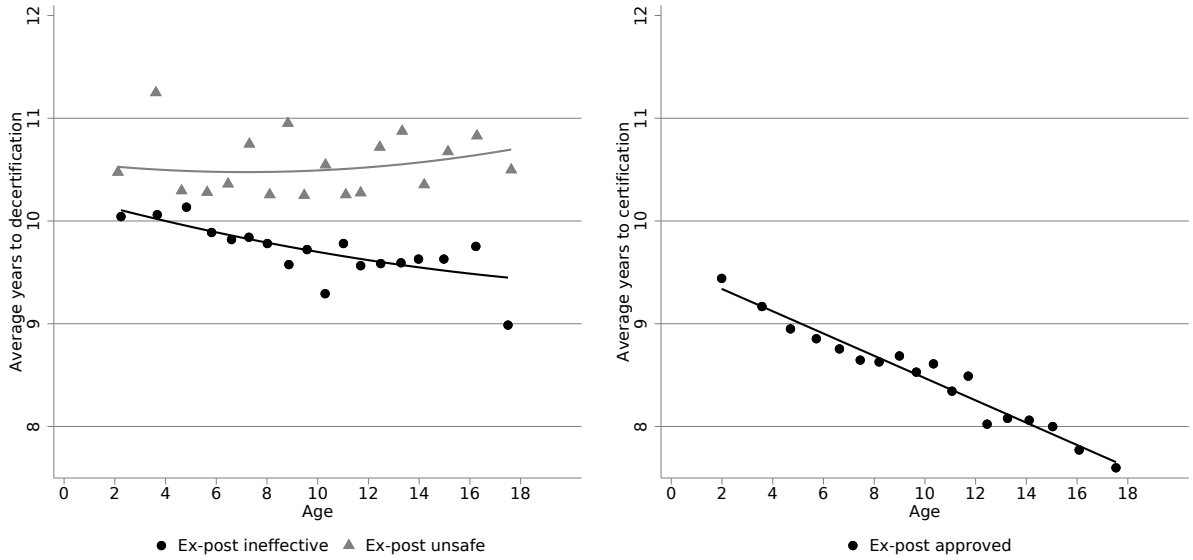
5.2 Timing of FDA certification and decertification events

Figure 3 shows the average number of years elapsed between initial drug approval and subsequent FDA certification and decertification events as a function of age for drug-disease pairs experiencing such an event. The left sub-figure in Figure 3 plots the average years elapsed since initial market entry for drug-disease pairs eventually documenting an ineffective or unsafe finding, whereas the right sub-figure plots the average time between initial drug approval and subsequent FDA approvals. As before, all figures control for disease fixed effects.

Figure 3 shows that, on average, a significant amount of time passes between initial drug approval and subsequent FDA certification or decertification events – less than 25% of all drug-disease pairs record a certification or decertification event within 5 years of initial market entry. This

[24]For example, if a drug label states "approved for children and adults", but does not specify ages for children, we assume it is approved for all pediatric ages.

Figure 3: Average years elapsed between initial drug approval and positive and negative events by age across drug-disease combinations

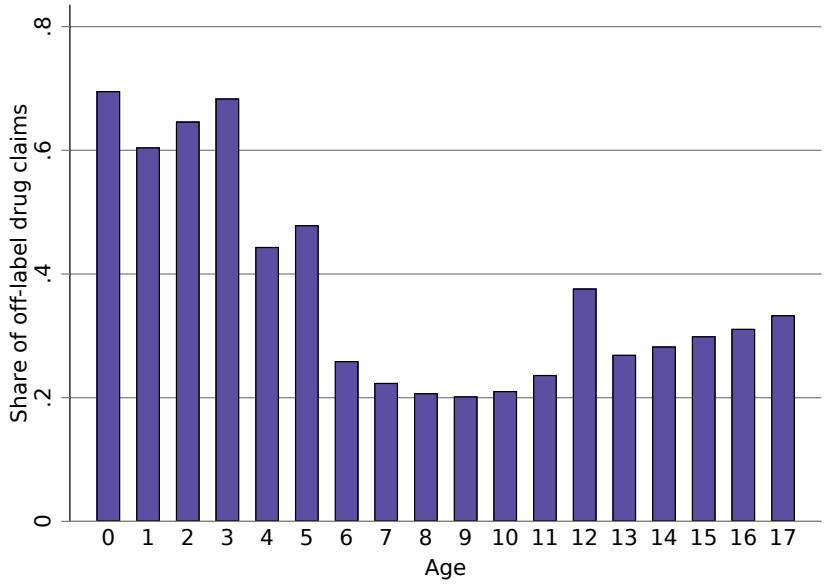


Note. The left sub-figure plots the average number of years since initial market entry for drug-disease pairs with a finding of inefficacy or lack of safety after initial market entry as a function of pediatric age. The right sub-figure plots the average number of years since initial market entry for drug-disease pairs with FDA approval at some point after initial market entry. The sample includes all new drugs approved by the FDA between 1998-2013 and includes all initial indications that were FDA-approved. Both figures include disease fixed effects. Data on indications and ages associated with certification and decertification events comes from MicroMedex database, Drugs@FDA, and FDA's Pediatric Labeling Changes database.

indicates that prior to any FDA decisions for unapproved pediatric age ranges that eventually end up getting tested, physicians can prescribe, experiment with, and learn about efficacy and safety for unapproved drugs for at least 8 years for the median drug. This also allows for a significant amount of time for the establishing of prescribing practices that may or may not be affected by subsequent FDA decisions. This is quite a meaningful duration given that physician decision-making as pertaining to prescribing has been established as "sticky", persistent, and inertial (Phelps, 2000; Janakiraman et al., 2008; Chandra et al., 2011).

Second, Figure 3 indicates that across pediatric age ranges, both certification and decertification events tend to occur sooner for older pediatric age ranges relative to younger ages, which is a function of pediatric indication expansions first targetting adolescents and then younger pediatric patients. Additionally, the left sub-figure in Figure 3 shows that results pertaining to inefficacy tend to be submitted to the FDA sooner than events pertaining to safety. Decertification events related to safety and efficacy for pediatric patients younger than 5 years may take up to 10 years after market entry to be reported to the FDA. This may be a function of the our definition of safety-related decertification event, which includes adverse events related to long-term safety, which

Figure 4: Share of drug claims that are off-label by pediatric age



Note. This figure plots the rates of FDA approved and unapproved uses of new drugs entering the pharmaceutical drug market during 1998-2013. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5.

mechanically requires patients to be followed for longer periods of time. Additionally, it may also reflect difficulty with recruitment of younger pediatric patients for participation in clinical trials.

Lastly, certification events tend to occur sooner than decertification events. This could reflect endogenous responses by the drug sponsor such as delays in reporting due to fears of negative market response or attempts to further investigate the drug in modified clinical trials until a successful result is achieved.

5.3 Rates of off-label use

Among drug claims to pediatric patients, 22% of all drug claims are for off-label uses. This estimate is in line, if not lower, with other studies measuring pediatric off-label prescribing in various settings (Corny et al., 2015; Yackey et al., 2019; Cuddy and Currie, 2020). Figure 4 shows that the share of drug claims prescribed to pediatric patients falls with age and is highest among patients younger than 5. This result may be partly mechanical – as shown in Section 5.1, patients younger than 5 are least likely to have a drug approved. There is also a slight increase in the share of off-label drugs at age 12 since many sponsors initially test drugs among adolescents, often defined as 13-17 year olds.

Table 1 shows the drugs with the highest on-label and off-label drug claims (as a share of total drug claims to the drug) prescribed among children (0-11 years of age) and adolescents (12-17 years of age). Since many drugs have few pediatric prescriptions, to construct this table we only consider drugs in the top decile (¿35,000 drug claims) in terms of number of pediatric drug claims.

As shown in the left panel of Table 1, for pediatric patients younger than 12, the most frequently used on-label drugs mainly include drugs used to treat attention deficit hyperactivity disorder (ADHD), allergies, asthma, and skin and ear infections (idiopathic urticaria and otitis media/externa). Among adolescents, the most frequently used on-label drugs include drugs indicated for treatment of asthma, allergies, ADHD, and skin and ear infections, but also include drugs indicated for the treatment of acne and autoimmune conditions such as ankylosing spondylitis, Crohn's disease, psoriasis, rheumatoid arthritis, and ulcerative colitis. With the exception of infliximab, all of the top on-label drugs among both children and adolescents were approved for some pediatric age range at initial market entry.

The right panel of Table 1 shows the ten most frequently used off-label drugs among children and adolescents. Two out of the ten drugs with the highest off-label use rates among children are among the most frequently used on-label drugs in adolescents and are used to treat asthma (budesonide + formoterol and levalbuterol), suggesting that some share of off-label use in children is for drugs approved in adolescents but not younger ages. Additionally, two of the ten drugs with the highest off-label drug claims among children are used to treat depression or anxiety (citalopram and escitalopram). Similarly, among adolescents, mental health drugs are among the most frequently used drugs with highest off-label shares, consistent with studies on off-label use rates across disease areas. In fact, four out of the top ten are used to treat mental health conditions (citalopram, duloxetine, escitalopram, and aripiprazole). While escitalopram was approved for treatment of depression in adolescents in the last four years of our data, citalopram has never been approved for treatment of depression in any pediatric age. Aripiprazole was approved for pediatric treatment of autism, bipolar disorder, Tourette's, and schizophrenia in the last 7 years of our data, and duloxetine was never approved for any pediatric age ranges during the span of our data (although it was approved for anxiety and fibromyalgia after 2013). The high rate of off-label use among these mental health drugs in adolescents indicates that either they are being used for treatment of eventually-approved indications prior to approval or are used for treatment of other conditions not approved by the FDA. To solely isolate off-label uses for indicated conditions but for unapproved ages, our subsequent analyses exclude off-label uses among patients never diagnosed with an indicated condition, as discussed in Section 4.5.

Table 1: Top ten on-label and off-label drugs for children and adolescents

Children (0-11 years of age)

Top 10 on-label drugs			**Top 10 off-label drugs**		
Drug name	*% on-label*	*Indicated for*	*Drug name*	*% off-label*	*Indicated for*
lisdexamfetamine	90%	ADHD	budesonide + formoterol	100%	Asthma
levothyroxine	88%	Hypothyroidism; Myxedema coma; Thyroid cancer	polyethylene glycol	100%	Constipation
levocetirizine	88%	Idiopathic urticaria; Allergic rhinitis	zonisamide	100%	Partial seizures
ciprofloxacin + dexamethasone	86%	Otitis media and externa	moxifloxacin	100%	Chronic bronchitis; Conjunctivitis; Acute sinusitis; Pneumonia; Skin infections; Abdominal infections; Plague
fluticasone + salmeterol	86%	Asthma; Chronic bronchitis	citalopram	100%	Depression
dexmethylphenidate	86%	ADHD	benzoyl peroxide + clindamycin	100%	Acne
ciprofloxacin + hydrocortisone	84%	Otitis externa	escitalopram	100%	Depression; Anxiety
atomoxetine	84%	ADHD	levalbuterol	48%	Asthma
oxcarbazepine	79%	Partial seizures	pimecrolimus	45%	Atopic dermatitis
ciclesonide	70%	Asthma; Allergic rhinitis	desloratadine	34%	Idiopathic urticaria; Allergic rhinitis

Adolescents (12-17 years of age)

Top 10 on-label drugs			**Top 10 off-label drugs**		
Drug name	*% on-label*	*Indicated for*	*Drug name*	*% off-label*	*Indicated for*
clindamycin + tretinoin	95%	Acne	citalopram	100%	Depression
budesonide + formoterol	93%	Asthma	moxifloxacin	100%	Chronic bronchitis; Conjunctivitis; Acute sinusitis; Pneumonia; Skin infections; Abdominal infections; Plague
adapalene + benzoyl peroxide	93%	Acne	polyethylene glycol	100%	Constipation
ciprofloxacin + hydrocortisone	93%	Otitis externa	duloxetine	100%	Depression; Anxiety; Fibromyalgia; Pain
ciprofloxacin + dexamethasone	92%	Otitis media and externa	aripiprazole	63%	Autistic disorder; Bipolar disorder; Tourette's; Depression; Schizophrenia
levocetirizine	90%	Idiopathic urticaria; Allergic rhinitis	pantoprazole	56%	Erosive esophagitis; GERD; Gastric hypersecretion; Zollinger-Ellison syndrome
dexmethylphenidate	90%	ADHD	oxycodone	51%	Pain
infliximab	90%	Ankylosing spondylitis; Crohn's disease; Plaque psoriasis, Psoriatic arthritis; Rheumatoid arthritis; Ulcerative colitis	escitalopram	50%	Depression; Anxiety
levalbuterol	89%	Asthma	lisdexamfetamine	50%	ADHD; Binge eating disorder
atomoxetine	87%	ADHD	levetiracetam	23%	Partial and generalized seizures

Note. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Percent on-label refers to the share of all drug claims that are for FDA-approved uses, conditional on having at least 1000 drug claims per drug. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5.

6 Results

6.1 Adoption of FDA-approved and unapproved uses at initial market entry

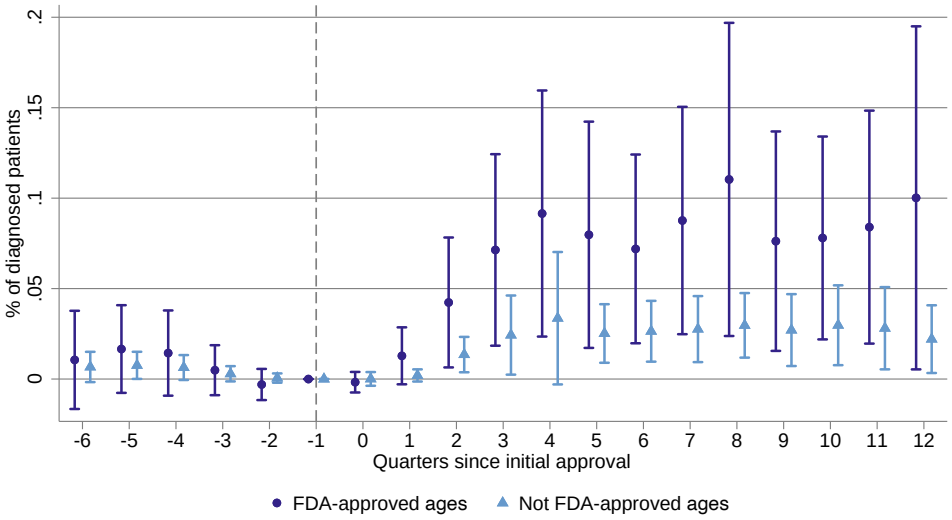
Figure 5 shows the effect of *initial* FDA approval on the probability of a pediatric patient diagnosed with an FDA-approved disease receiving a newly approved drug and the drug adoption rate for newly approved drugs in FDA-unapproved ages. This figure separately plots the effect of initial FDA approval on FDA approved uses vs. off-label (FDA unapproved) uses, which can include untested, unproven, and unapproved uses of the drug, as well as those that are ex-post tested, regardless of the ex-post outcome.

As shown in Figure 5, conditional on patient characteristics, patients and physicians adopt a drug even in the absence of FDA certification for the use. The rate of FDA-unapproved uses steadily increases during the first year after initial market entry and remains constant and statistically significantly positive at 0.05% for the following three years – we find no evidence of de-adoption of FDA-unapproved uses. Since data used to estimate these parameters only includes time periods when no subsequent FDA certification or decertification events for pediatric events occurs, this figure isolates the drug adoption in the absence of subsequent FDA information. Although the increase in FDA-unapproved uses is small in absolute magnitude (0.05% increase), 70% of patients diagnosed with diseases in our data are never treated with pharmaceuticals and the average therapeutic drug class has 40 drugs, indicating that market shares per drug are low and a 0.05% increase is economically meaningful. Figure 5 provides suggestive evidence that one side of the tradeoff of regulatory (in)action – untested drugs being prescribed to patients – indeed occurs in practice.

Second, Figure 5 shows that an FDA approval for a pediatric age at the time of initial market entry is clearly informative and valuable to patients and physicians. Conditional on patient and plan characteristics, FDA approved uses in pediatric patients are prescribed at twice the rate of unapproved uses. This difference in the rate of FDA-approved vs. FDA-unapproved uses starts from the very moment of market entry and continues for the remainder of the first year since market entry. The on-label use rates also stabilize after the first year since initial approval at approximately 0.1% of all diagnosed patients.

Figure 6 shows that neither FDA-approved uses nor FDA-unapproved uses cannibalize market shares of existing drugs in a similar therapeutic class as the entrant – almost all of the prescribing of newly approved drugs, regardless of whether the drug was approved for pediatric age ranges or not, occurs among treatment naive patients who have never been treated with another drug in the same therapeutic class as the entrant. The finding that npatients who have never been treated with other drugs in a similar therapeutic class as the entrant start with an FDA-unapproved use is surprising since the therapeutic classes corresponding to sample drugs in our data on average encompass 40 drugs; thus many alternatives are available. However, it is possible that other competitors of the entrant within the same therapeutic class are also not approved for pediatric ages, so this finding

Figure 5: Drug adoption at initial market entry



Note. This figure plots the rates of FDA approved and unapproved uses of new drugs entering the pharmaceutical drug market during 1998-2013. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, patient treatment experience fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

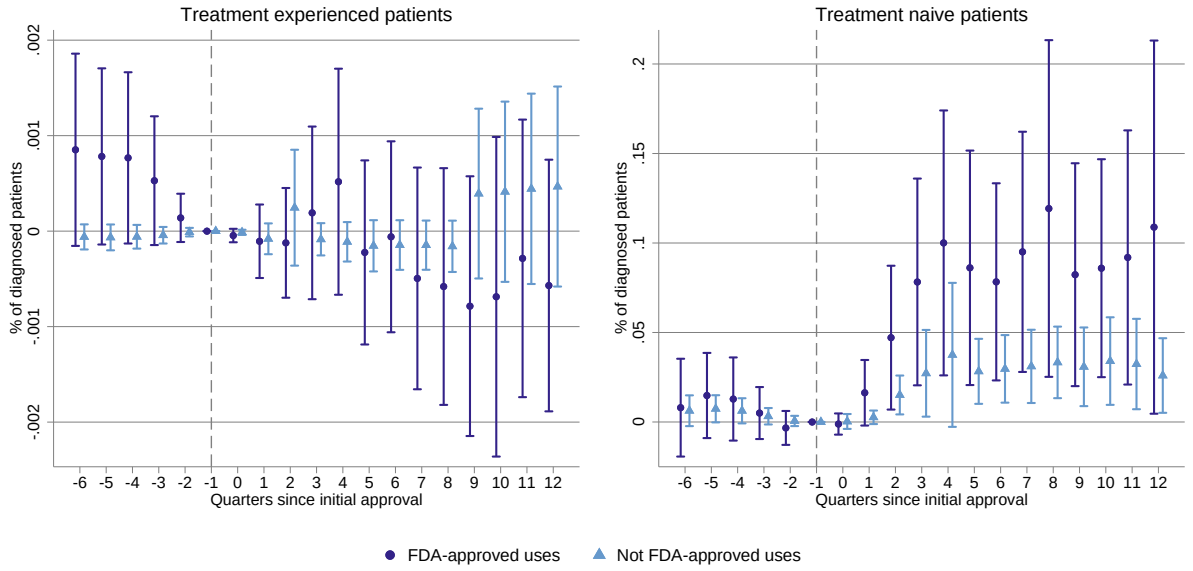
may not necessarily correspond to substitution away from FDA-approved uses.[25]

Additionally, Figure 7 shows that conditional on plan and patient characteristics, drug uses without FDA-approval occur both among patients with high and low health care utilization rates. If we take health care utilization rates, specifically the occurrence or prior emergency room (ER) visits and hospitalizations as a proxy for disease severity, Figure 7 shows that even though the overall rate of prescriptions for newly approved drugs is twice as high among the more severely affected patients who have at least one claim for an ER or hospital visit prior to receiving the drug, the rate of FDA-unapproved uses is statistically significantly non-zero for the less severe patients as well, indicating that FDA-unapproved uses may not necessarily be targeted solely towards more severe patients.

Lastly, we find small differences in adoption of off-label uses between more and less restrictive plans, as shown in Figure A1, although on-label use rates are higher among patients in less restrictive plans.

[25] Unfortunately, we do not have data on indications for competitors to our sample drugs and thus cannot determine whether substitution of this sort is occurring.

Figure 6: Drug adoption at initial market entry by patient treatment status



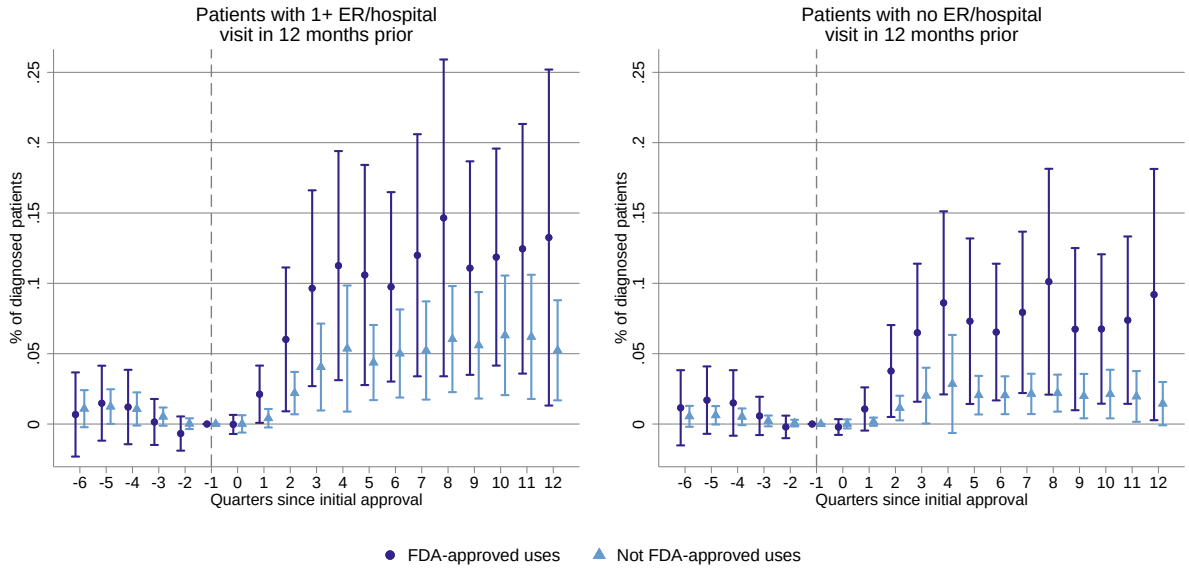
Note. This figure plots the rates of FDA approved and unapproved uses of new drugs entering the pharmaceutical drug market during 1998-2013 by patient treatment status. Treatment experienced patients were defined as those with at least one drug claim for a drug in the same therapeutic drug class as the newly approved drug prior to receiving the newly approved drug. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

6.2 Drug adoption at initial market entry as a function of ex-post outcomes

To examine what types of off-label drugs are adopted by physicians, Figure 8 plots the rates of drug adoption, similar to Figure 5, broken down by whether the drug was ex-post found to be effective, ex-post ineffective or unsafe (combined into a single category to improve precision of our estimates), or never tested. Since this figure includes drug adoption at initial market entry conditional on *not* being approved at initial market entry, all drug adoption rates plotted in this figure refer to off-label rates. As previously, time periods where subsequent FDA certification or decertification occurs are excluded from estimation and estimates encompass drug adoption in the absence of subsequent FDA labeling changes.

First, Figure 8 shows that physicians and patients deciding to prescribe off-label drugs are largely adopting drugs that are later shown to be effective. Such drugs are being prescribed at an increasing rate continuing into three years after the initial drug approval and prior to any subsequent FDA decisions, reaching 0.01% of all diagnosed patients by the end of the third year since market entry. The adoption of ex-post effective drugs does not appear to slow down with time; however, our

Figure 7: Drug adoption at initial market entry by patient health care utilization



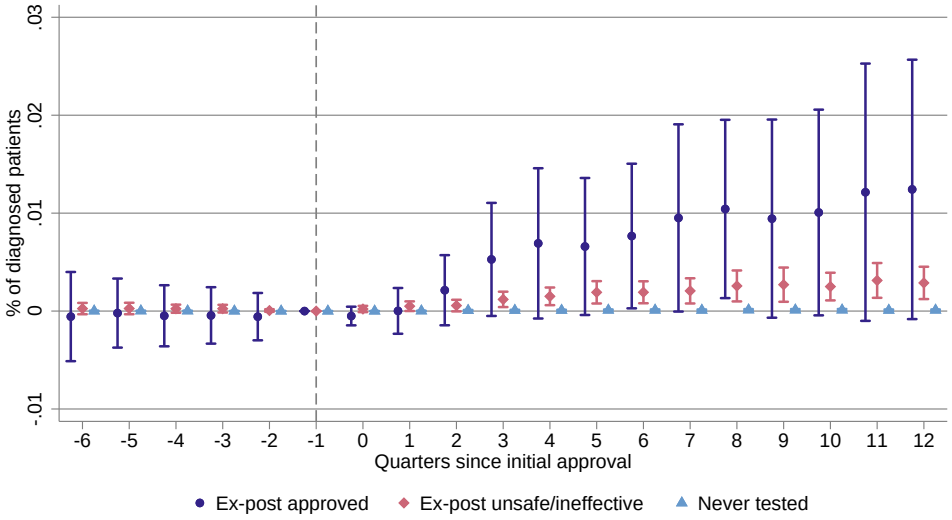
Note. This figure plots the rates of FDA approved and unapproved uses of new drugs entering the pharmaceutical drug market during 1998-2013 by emergency room (ER) and hospital utilization of the patient in the 12 months prior to the drug claim. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, patient treatment experience fixed effects, and plan fixed effects at the time of drug claim.

estimates for these types of drugs are imprecisely estimated.

Additionally, Figure 8 shows that drugs that are ex-post shown to be unsafe or ineffective are gradually adopted starting during the first year since market entry. Although the rate is much lower than ex-post effective drugs, it is precisely estimated and statistically significantly non-zero by the end of the first year since market entry. Figure 8 also shows that drugs that are never tested are not adopted, likely because such drugs are used in diseases mostly affecting adults (and are waived from PREA requirements).

Appendix Figure A2 and Figure A3 show that drug claims for both ex-post effective and ex-post ineffective/unsafe drugs are targeted primarily towards treatment naive patients and there appears to be no difference in the adoption of ex-post inefective drugs across plan types. Interestingly, Appendix Figure A4 shows that while rates of off-label use of ex-post effective and safe drugs is similar between more severe and less severe patients, ex-post unsafe/ineffective drugs are primariy prescribed to more severe patients. This may suggest that physicians are willing to try treatments for more severe patients that may not work for the average clinical trial patient.

Figure 8: Drug adoption at initial market entry by ex-post outcomes



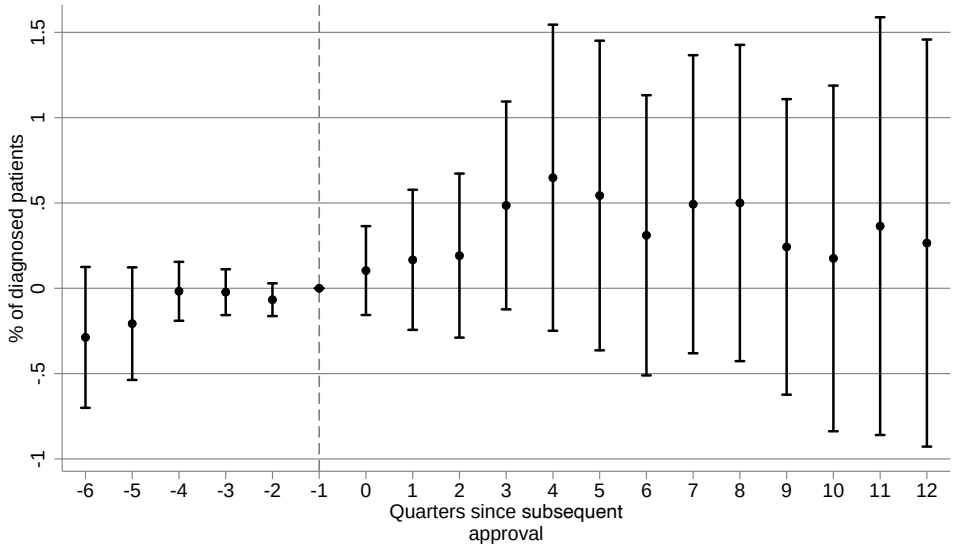
Note. This figure plots the off-label rates of new drugs entering the pharmaceutical drug market during 1998-2013 by ex-post FDA certification or decertification events. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on indications and ages associated with certification and decertification events comes from MicroMedex database, Drugs@FDA, and FDA's Pediatric Labeling Changes database. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, patient treatment experience fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

These findings highlight two sides of the lack of regulatory action in this setting. First, physicians appear to accurately adopt ex-post effective drugs, indicating that the existence of off-label use even in the absence of subsequent FDA action is valuable to patients as it allows for earlier access to effective drugs. On the other hand, a positive share of patients receive a drug that is ex-post shown to be ineffective or unsafe, indicating that the absence of regulatory action allows for adoption of harmful drugs.

6.3 Event study at subsequent FDA (de)certification

Given that even prior to subsequent trials we observe physicians and patients taking off-label drugs, we investigate whether subsequent FDA certification or decertification of drugs has an impact on demand for drugs or whether physicians who would have adopted the drug under FDA certification already adopted it as part of their off-label prescribing practice. Figure 9 shows the event study results at *FDA certification* for subsequent pediatric ages beyond ages approved at market entry, controlling for time the drug has been on the market as well as patient characteristics. This figure suggests that subsequent approvals increase the rate of new prescriptions slightly, although this

Figure 9: Drug demand at subsequent FDA certification



Note. This figure plots the prescribing rates for drugs approved between 1996-2013 around FDA certification (approval) for some pediatric age. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, patient treatment experience fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

increase is imprecisely estimated.[26] In fact, Figure 10 suggests that the drug already had a large off-label market share in the newly approved disease and age range and most drug claims simply get reclassified as on-label upon FDA approval, indicating that the same patients continue taking the drug even after FDA approval.

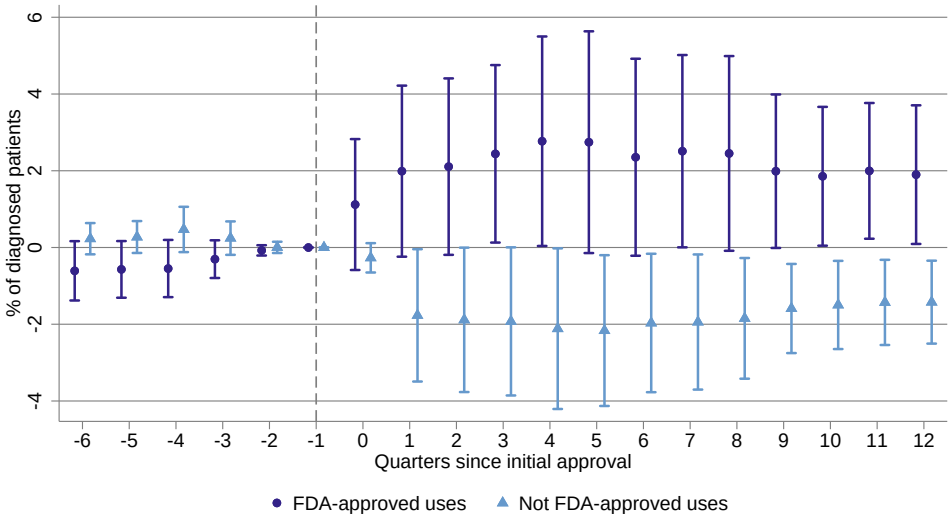
Figure 11 shows our event study estimates around *FDA decertification* events, i.e., addition of negative trial results to the drug label. This figure shows that the addition of a negative trial result for a specific disease and age range has no impact on the demand for the decertified drug in the disease and ages which had a negative result. There does appear to be some de-adoption of the drug starting in the third year after the negative result, though this is also imprecisely estimated.

7 Discussion and conclusion

Our findings suggest that while physicians adopt drugs in pediatric patients without corresponding FDA labeling information, the majority of these prescriptions are for drugs that are ex-post shown to be effective. However, in equilibrium, physicians continue prescribing ex-post unsafe/ineffective

[26] We do not observe any patient groups that see a precisely estimated increase, as shown in Appendix Figure A5-Figure A7.

Figure 10: Drug demand at subsequent FDA certification by approved vs. unapproved uses

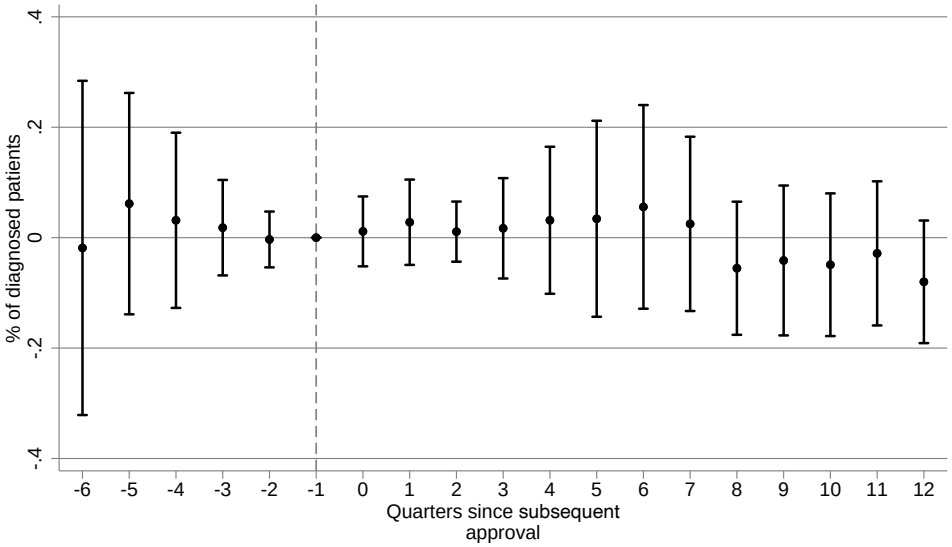


Note. This figure plots the prescribing rates for drugs approved between 1996-2013 around FDA certification (approval) for some pediatric age. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, patient treatment experience fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

drugs. FDA labeling changes adding such negative results to the drug label have little impact on decreasing such potentially harmful and costly uses; positive labeling changes slightly increase prescribing.

We find, however, that, conditional on drug treatment, more severe patients as measured by prior ER and hospital use have a larger share of drug claims for ex-post ineffective or unsafe drugs. Clinical trial results typically reflect treatment effects for the average enrolled patient. Off-label uses of may be effective for some patients and thus non-zero off-label uses in equilibrium may not necessarily be welfare reducing. Welfare calculations weighing the benefits and the costs of pediatric labeling changes are further complicated by the wide array of conditions included in the analysis for which there is no consistent endpoint used to measure outcomes. Extensions of this work will focus on (a) estimating the direct impact of off-label use on patient utilization and outcomes identifiable in insurance claims data and (b) combining data on clinical trial costs and estimated benefits to quantify returns to pediatric labeling with and without extensive delays in such labeling changes.

Figure 11: Drug demand at subsequent FDA decertification



Note. This figure plots the prescribing rates for drugs approved between 1996-2013 around FDA decertification (addition of a negative trial result to the drug label) for some pediatric age. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, patient treatment experience fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

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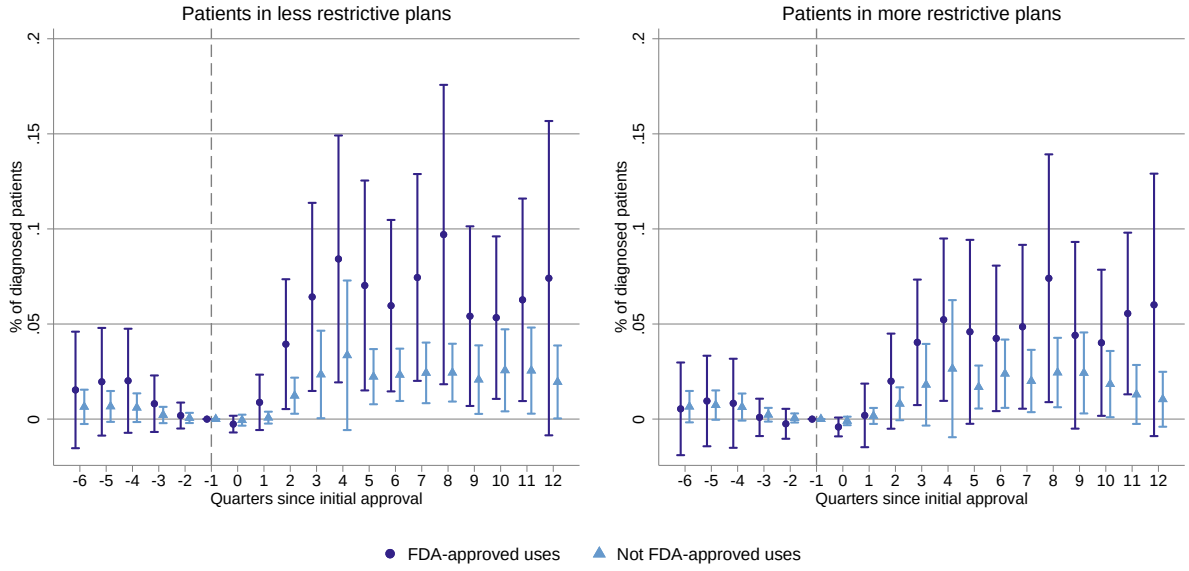
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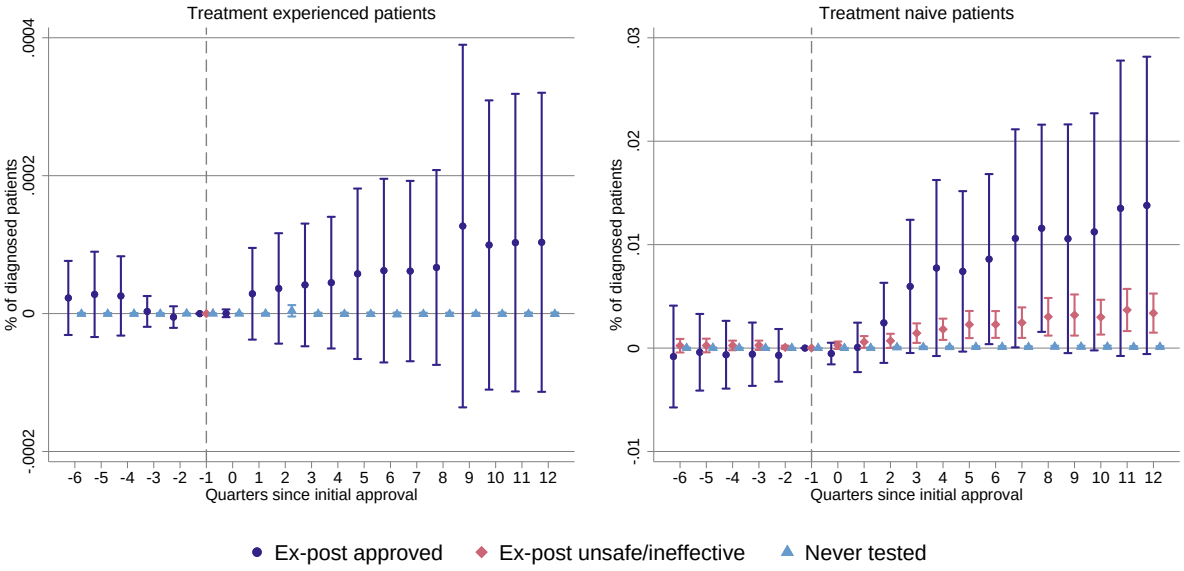
Appendix Tables and Figures

Appendix Figure A1: Drug adoption at initial market entry by patient plan enrollment



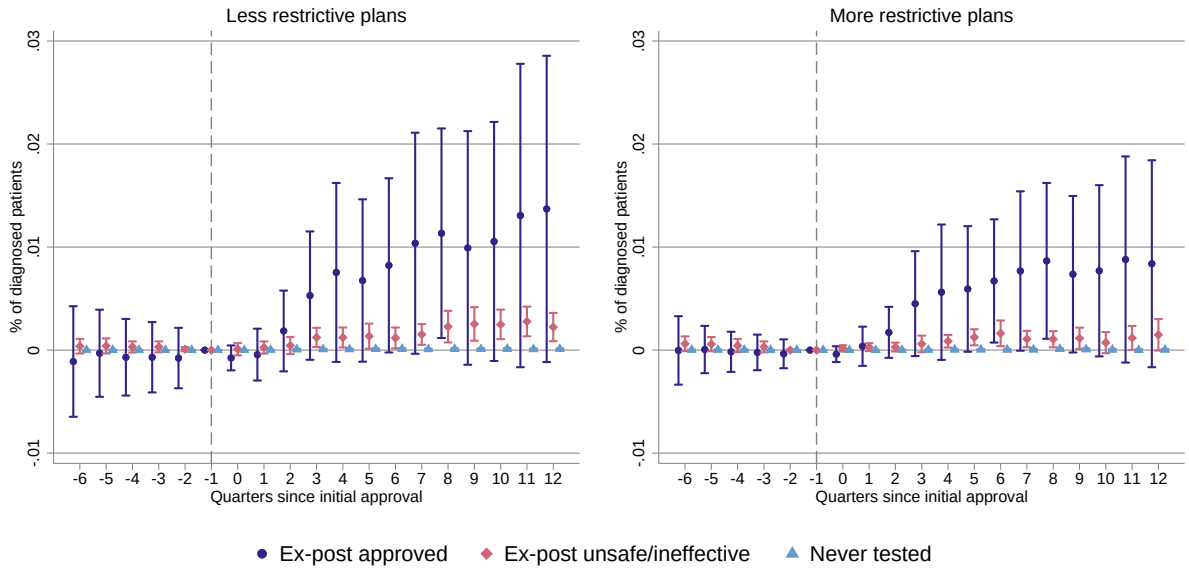
Note. This figure plots the rates of FDA approved and unapproved uses of new drugs entering the pharmaceutical drug market during 1998-2013 by patient plan enrollment. Less restrictive plans include all Preferred Provider Organization (PPO) plans and more restrictive plans include all Health Maintenance Organization (HMO) plans. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

Appendix Figure A2: Drug adoption at initial market entry by ex-post outcomes and patient treatment status



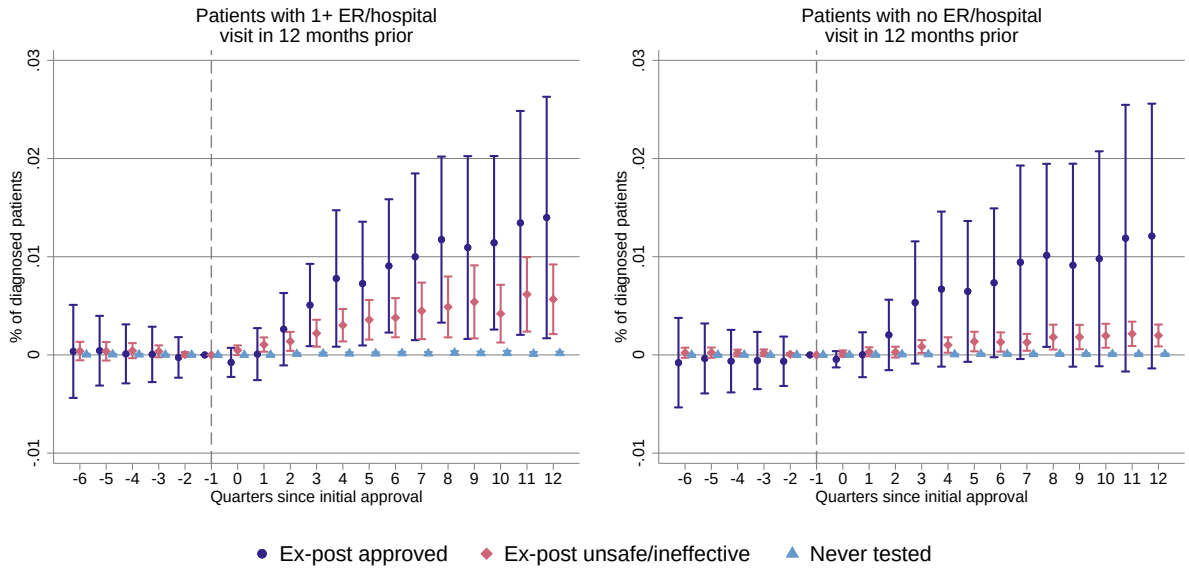
Note. This figure plots the off-label rates of new drugs entering the pharmaceutical drug market during 1998-2013 by ex-post FDA certification or decertification events and by patient treatment status. Treatment experienced patients were defined as those with at least one drug claim for a drug in the same therapeutic drug class as the newly approved drug prior to receiving the newly approved drug. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

Appendix Figure A3: Drug adoption at initial market entry by ex-post outcomes and patient plan enrollment



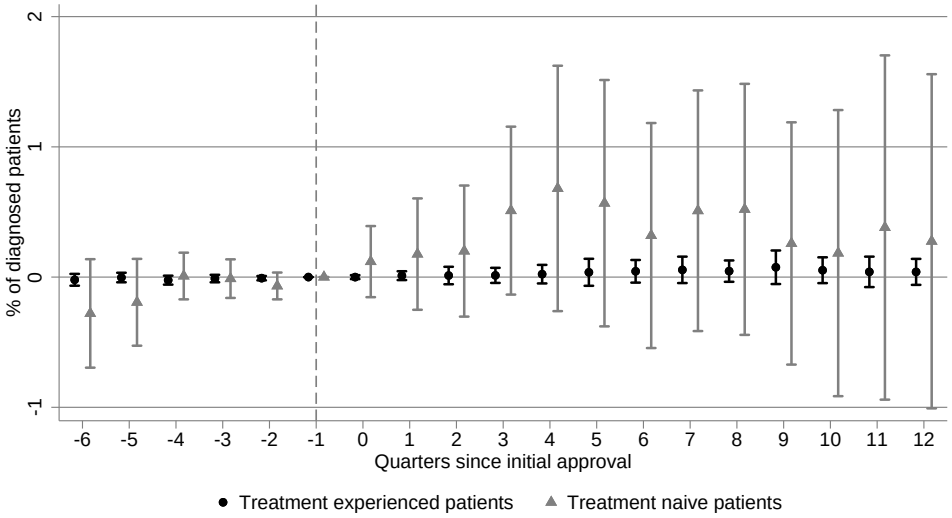
Note. This figure plots the off-label rates of new drugs entering the pharmaceutical drug market during 1998-2013 by ex-post FDA certification or decertification events and by patient plan enrollment. Less restrictive plans include all Preferred Provider Organization (PPO) plans and more restrictive plans include all Health Maintenance Organization (HMO) plans. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

Appendix Figure A4: Drug adoption at initial market entry by ex-post outcomes and patient health care utilization



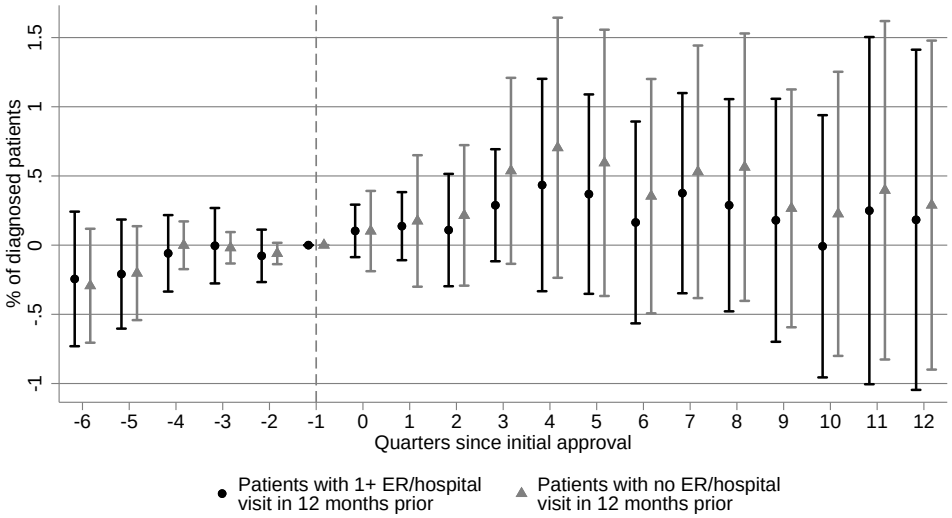
Note. This figure plots the off-label rates of new drugs entering the pharmaceutical drug market during 1998-2013 by ex-post FDA certification or decertification events and by emergency room (ER) and hospital utilization of the patient in the 12 months prior to the drug claim. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

Appendix Figure A5: Drug demand at subsequent FDA certification by patient treatment status



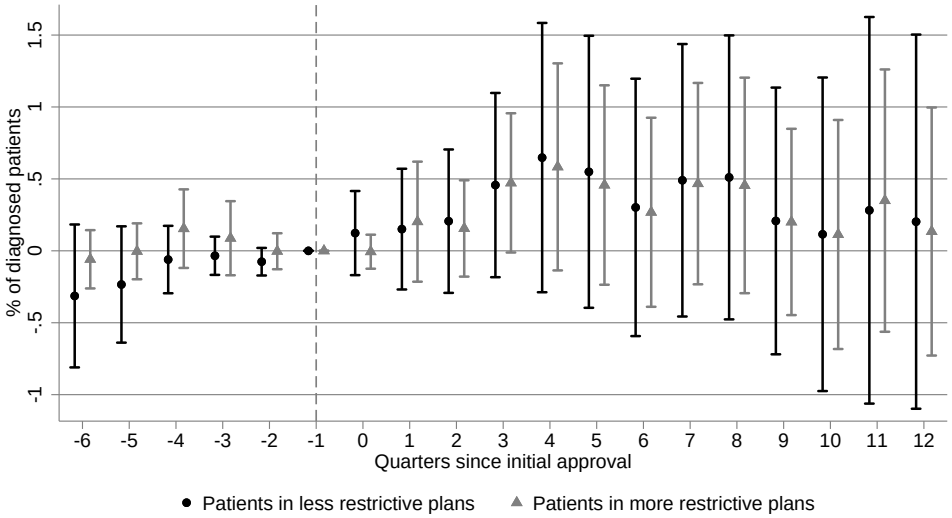
Note. This figure plots the prescribing rates for drugs approved between 1996-2013 around FDA certification (approval) for some pediatric age. Treatment experienced patients were defined as those with at least one drug claim for a drug in the same therapeutic drug class as the approved drug prior to receiving the drug. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, patient treatment experience fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

Appendix Figure A6: Drug demand at subsequent FDA certification by patient health care utilization



Note. This figure plots the prescribing rates for drugs approved between 1996-2013 around FDA certification (approval) for some pediatric age by emergency room (ER) and hospital utilization of the patient in the 12 months prior to the drug claim.. Treatment experienced patients were defined as those with at least one drug claim for a drug in the same therapeutic drug class as the approved drug prior to receiving the drug. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, patient treatment experience fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.

Appendix Figure A7: Drug demand at subsequent FDA certification by patient plan enrollment



Note. This figure plots the prescribing rates for drugs approved between 1996-2013 around FDA certification (approval) for some pediatric age. Less restrictive plans include all Preferred Provider Organization (PPO) plans and more restrictive plans include all Health Maintenance Organization (HMO) plans. Treatment experienced patients were defined as those with at least one drug claim for a drug in the same therapeutic drug class as the approved drug prior to receiving the drug. Drug claims were measured among pediatric patients (younger than 18 years of age) diagnosed with the FDA-approved diseases at initial market entry in the 1998-2013 MarketScan insurance claims data base. Data on approved indications and ages comes from MicroMedex database and Drugs@FDA. For a definition of FDA-approved vs. unapproved uses, see section Section 4.5. Models include drug-class-disease fixed effects, calendar time fixed effects, patient age by sex fixed effects, patient treatment experience fixed effects, plan fixed effects at the time of drug claim, and fixed effects for whether the patient had an emergency room or hospitalization claim during the 12 months prior to receiving the drug.