

Who Cares About a Label? The Effect of Pediatric Labeling Changes on Prescription Drug Utilization

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Abstract

Off-label drug use is common, particularly in pediatric populations. In response, legislation requires and/or provides financial incentives for drug manufacturers to perform pediatric clinical trials. Using New Hampshire's all-payer claims database, we examine the impact of subsequent changes to drug labeling on pediatric drug utilization. To separate changes in utilization induced by labeling changes from other temporal factors, we estimate difference-in-differences models that compare utilization trends for pediatric patients to those of adults. We estimate that establishing safety and efficacy increases a drug's market share by (a statistically significant) 2.8 percentage points, whereas failure to do so decreases a drug's market share by (a statistically insignificant) 0.9 percentage points. We then interpret these estimates within the context of public and market incentives to conduct pediatric clinical trials.

JEL Classifications: I11, I18

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1 Introduction

When a drug is prescribed for a purpose not explicitly approved by the Food and Drug Administration (FDA), the prescription is termed “off-label.”¹ Off-label drug use is common: estimates suggest that roughly one in five prescriptions in the United States is off-label (Radley et al. (2006)). For some patient populations and diseases, there may be no FDA approved treatments, or the approved treatments may prove unsafe and ineffective for specific patients. Existing drugs that treat related illnesses may provide an alternative, even if they have not undergone formal testing for the off-label use.²

While drug manufacturers are free to pursue additional clinical trials for new indications – potentially shifting any off-label use to on-label use – policymakers have expressed concerns that the amount of clinical research designed to produce information for off-label uses is insufficient.³ One of the barriers to clinical research of off-label uses is that drug manufacturers may have limited financial incentives to perform that research. Given the limited patent length for prescription drugs, manufacturers may find it difficult to capture the value of additional clinical trials. Indeed, the utilization of off-patent drugs for which new uses have been found is a common form of off-label use (Stafford (2008)). Even with patent protection, drug manufacturers may choose not to perform trials for all possible uses of a drug because the potential market size may be small and/or demand may not be sufficiently responsive to labeling information.

Off-label drug use is particularly common for pediatric patients. Historically, drug manufacturers infrequently collected and disseminated information on whether their drugs would safely and effectively treat children. For example, only 22 percent of drugs in the 1973 Physicians’ Desk Reference included pediatric prescribing guidelines, such as pediatric-specific safety, efficacy, and/or dosing instructions (Wilson (1975)). This dearth of pediatric-specific clinical information led to Dr. Harry Shirkey coining the term “therapeutic orphans” to describe pediatric patients who were excluded from FDA-approved uses of many prescription drugs (Shirkey (1968)). The lack of evidence on pediatric use did not substantively improve

¹We use the terminology “indication” to describe the specific disease and patient population for which a drug is intended to be used. FDA drug approvals are often for relatively specific populations, and may therefore exclude certain age ranges and/or sexes, pregnant women, women who are breastfeeding, and patients with certain comorbidities. Any alterations in the use of a drug from its FDA-approved use constitute off-label use.

²There is an ongoing debate about the appropriateness of widespread off-label drug use. For recent research comparing the efficacy of FDA-approved and off-label therapies, see, e.g., Ladanie et al. (2018).

³See, e.g., Addressing the Barriers to Pediatric Drug Development: Workshop Summary, Institute of Medicine 2008.

over the next twenty years. Only 20 percent of new molecular entities approved in 1995 with a potential pediatric use included labeling information specific to pediatric patients (Wilson (1999)). Given the relative lack of pediatric labeling, pediatric patients often take drugs off-label. Bazzano et al. (2009) report that 62 percent of outpatient pediatric visits between 2001 and 2004 included off-label prescribing. Kimland and Odland (2012) document that the majority of children in both hospital and primary care settings receive at least one off-label prescription.

Legislation in the US – the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) – seeks to reduce off-label pediatric prescribing by requiring and/or providing financial incentives for drug manufacturers to perform pediatric clinical trials. BPCA is often referred to as the “carrot” – because it offers manufacturers six months of additional market exclusivity in exchange for conducting pediatric trials – whereas PREA is often referred to as the “stick” – because it requires manufacturers in many cases to conduct pediatric trials in order to receive FDA approval for adult use. (See Section 1.1 below for a more comprehensive discussion of the legislation.) Hundreds of drugs with a potential use in pediatric populations now have updated drug labels that contain information specific to pediatric use. This paper investigates the value of that updated labeling information, as measured by changes in pediatric drug utilization following labeling changes. The paper thus contributes to the literature examining the impact of clinical trial results and/or FDA actions on the provision of healthcare services (see, e.g., Lamas et al. (1992); Azoulay (2002); Calvo and Rubinstein (2002); Price and Simon (2009); Dorsey et al. (2010); Dusetzina et al. (2012)).

For a sample of drugs that experienced pediatric labeling changes between 2009 and 2011, we examine the impact of labeling changes on subsequent drug utilization using New Hampshire’s all-payer claims database.⁴ We define positive labeling changes as those for which safety and efficacy were established, and negative labeling changes as those for which either safety and/or efficacy were not established. To separate changes in utilization induced by labeling changes from other temporal factors, we exploit the fact that the labeling changes associated with the legislation are specific to the pediatric population. Difference-

⁴Instead of examining utilization, an alternative approach to studying the value of pediatric testing is to explore whether pediatric clinical trials affect the frequency with which adverse outcomes are reported in children. However, as the reporting of adverse outcomes is relatively uncommon and children often represent a small patient population, available adverse outcomes data may be inadequate for that purpose (see the appendix for more details on the availability of adverse event data for our specific sample of drugs). Instead, this study relies upon revealed preferences, which should incorporate, for example, changes in physician prescribing behavior resulting from anticipated changes in the likelihood of adverse events.

in-differences models comparing utilization trends for children to those of adults indicate a (statistically significant) 2.8 percentage point increase in market share for drugs with a positive labeling change and a (statistically insignificant) 0.9 percentage point decrease in market share for drugs with a negative labeling change. Given a baseline share of about 23 percent, the positive labeling changes correspond to a 12 percent increase in market share. We also find suggestive evidence of (i) learning about safety and efficacy prior to labeling changes and (ii) larger utilization responses for cases in which competing drugs have not yet produced pediatric labeling information.

While these estimates are specific to the New Hampshire population, the primary benefit of the data is that it is publicly available. Alternative proprietary datasets, such as Truven’s MarketScan database, are appealing sources for a similar analysis, but are less accessible to the broader research community. We therefore believe that the New Hampshire data provides a good starting point, though we of course welcome further exploration using other data sources.

To conclude the paper, we demonstrate how the utilization estimates can be applied to examine public and market incentives for producing pediatric labeling information. These calculations are by necessity back-of-the-envelope, and require extrapolating our results for New Hampshire to the rest of the country. While the specific numbers should therefore be interpreted with due caution, the calculations illustrate how the utilization effects can shed light on broader policy questions. In the first calculation, we compare estimates of drug manufacturer profits from increased utilization to external estimates of the costs of pediatric clinical trials. This exercise confirms that it would often be unprofitable for manufacturers to perform pediatric trials in the absence of legislation like BPCA and PREA. That said, to the extent that manufacturer profits do not align with social welfare, it is possible that pediatric clinical trials are good for consumers. In the second calculation, we quantify how much the utilization affected by pediatric labeling changes would need to be worth (in dollar terms) to outweigh the additional drug spending in the adult population due to the exclusivity provisions of BPCA. For the median drug, the benefit of the drug for the marginal pediatric patient must exceed the drug’s price by a factor of 3.5 – \$646 in dollar terms (2013 dollars) – to outweigh the cost to the adult population of extended exclusivity. There is, however, substantial heterogeneity in these estimates, driven in large part by differences between drugs in the relative sizes of the adult and pediatric populations.

The rest of the paper proceeds as follows. Section 1.1 provides more detail about current

legislation intended to foster pediatric clinical trials.⁵ Section 2 describes our data sources. Section 3 estimates the effect of labeling changes on utilization. Section 4 reports a variety of robustness checks. Section 5 examines the implications of the utilization estimates for policy. Section 6 concludes.

1.1 Additional legislative background and related research

The Best Pharmaceuticals for Children Act (BPCA), which became law in 2002, offers drug manufacturers six months of additional market exclusivity – beyond patent-based exclusivity – in exchange for conducting pediatric studies. To qualify for pediatric exclusivity, manufacturers must receive a written request from the FDA inviting further study of the drug in pediatric patients and then comply with the various terms of the FDA’s request (e.g., surrounding study design, ages of interest, etc.). Manufacturers satisfying the FDA’s written request receive exclusivity even if safety and efficacy are not established in the pediatric clinical trials. Importantly, exclusivity for performing pediatric trials applies to all uses of the drug, including in the adult population. The expanded scope of the exclusivity strengthens manufacturers’ financial incentives to undertake pediatric trials, even if the relevant pediatric population is small. Indeed, Olson and Yin (2017) find that manufacturers are more likely to accept a written request as the overall sales of a drug increase (holding the size of the pediatric population constant).

The Pediatric Research Equity Act (PREA), which became law in 2003, requires manufacturers to submit data assessing the safety and efficacy of the drug for pediatric patients as part of New Drug Applications. This requirement can be waived in certain circumstances, e.g. if the number of pediatric patients is negligible or the drug is likely to be dangerous to children. The FDA may also grant manufacturers a deferral from PREA requirements so that a drug can be approved for adults while the manufacturer performs pediatric trials.

Since the passage of BPCA and PREA, the share of drugs with pediatric prescribing guidelines has roughly doubled. Sachs et al. (2012) find that 46 percent of drugs in the 2009 Physicians’ Desk Reference and 41 percent of new molecular entities approved between 2002 and 2008 had pediatric prescribing guidelines. Pediatric studies that have been performed under BPCA and/or PREA vary in what types of information they provide. GAO (2011) finds that 76 percent of labeling changes expanded the approved age group to include pediatric patients (or additional pediatric ages). In 22 percent of cases, safety and efficacy of

⁵For a more complete discussion of the relevant legislation and its historical precedents, see, e.g., Field et al. (2012).

the drug were not established in the tested pediatric population. That said, it is uncommon for drugs to have very different safety profiles in pediatric and adult populations. For example, a boxed warning was inserted concerning pediatric use in only one of the 130 labeling changes studied by GAO (2011). Other studies have confirmed that most pediatric labeling changes expand the approved age group, and that safety and efficacy are not established in a minority of cases (Roberts et al. (2003); Benjamin et al. (2006); Rodriguez et al. (2008); Benjamin et al. (2009); Wharton et al. (2014)).

2 Data

2.1 Pediatric labeling changes: FDA database

The FDA maintains a database of pediatric labeling changes generated by BPCA and PREA.⁶ For each labeling change, the data contains the date, the brand name, the generic name, the indications studied, and a summary of the change, along with a link to the updated label. In cases where we were able to locate the time difference between (i) the manufacturer’s submission to the FDA with the pediatric trial evidence and (ii) the subsequent labeling change, the modal difference is about six months in our sample. Figure 1 documents the number of pediatric labeling changes that the FDA attributed to BPCA, PREA, or both over the 2003 to 2013 period. During this period, there were 38 labeling changes per year on average.

Some labeling changes disclose positive news about the drug whereas others disclose negative news. Figure 2 displays two recent examples. Safety and efficacy were established for Zerviate, whereas efficacy was not established for Simponi. In the empirical analysis, we classify all labeling changes as either “positive” or “negative.” Positive labeling changes correspond to drugs being found safe and effective in pediatric patients, whereas negative labeling changes correspond to drugs being found either unsafe or ineffective.⁷

This positive/negative binary classification scheme is coarser than the full level of detail available in the labeling changes. For instance, a drug may be safe but ineffective, which is presumably less negative than if the drug was both unsafe and ineffective. Or, perhaps a drug that was thought to be extremely effective was only found to be slightly effective,

⁶The data is publicly available online at the FDA’s website. (<https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>)

⁷For a small number of drugs, the labeling change specifies both positive and negative changes. For instance, the drug may have been established to be safe and effective for pediatric patients aged 12 to 17 but ineffective for younger patients.

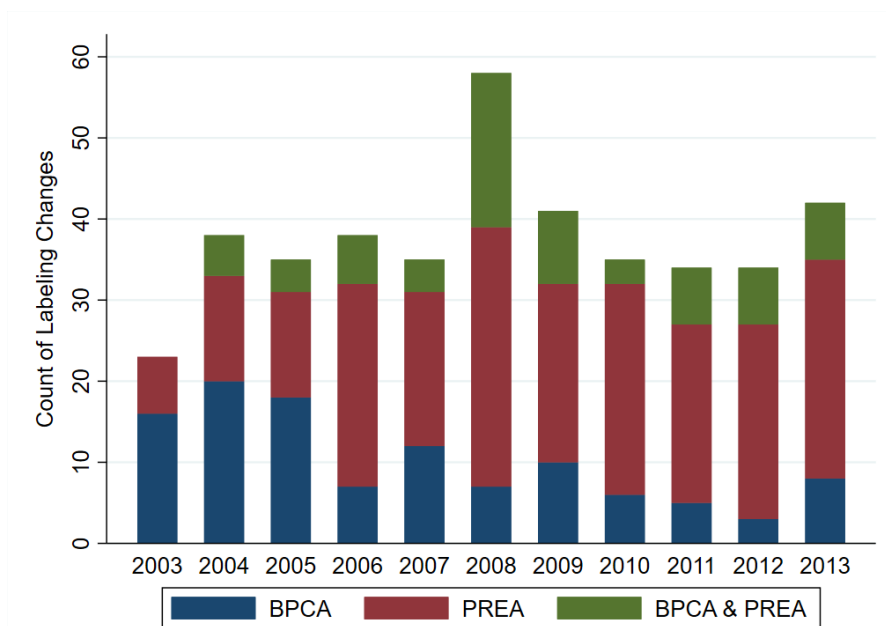


Figure 1: Number of Pediatric Labeling Changes Under BPCA & PREA, 2003-2013 The figure displays the count of pediatric labeling changes that occurred in each year that the FDA attributed to BPCA, PREA, or both. Some drugs experience multiple labeling changes.

Pediatric Labeling Date	Trade Name	Label Changes Summary
06/22/2017	Simponi	*Effectiveness in pediatric patients less than 18 years of age has not been established. *Safety and efficacy were evaluated in a multicenter, placebo-controlled, double-blind, randomized-withdrawal, parallel group study in 173 children 2 to 17 years of age
05/30/2017	Zerviate Ophthalmic Solution	*Safety and effectiveness have been established in pediatric patients two years of age and older. *Use in these pediatric patients is supported by evidence from adequate and well-controlled studies in pediatric and adult patients.

Figure 2: FDA Pediatric Labeling Data Examples

which we would classify as a positive change although it may have constituted a negative change relative to expectations. Rigorously defining gradations of safety and efficacy – and/or measuring physician expectations about a drug prior to a pediatric labeling change – is beyond the scope of the present paper. In addition, given the relatively limited sample size (as discussed in more detail in the next several subsections), statistical power also constrains any efforts to examine more detailed differences between labeling changes.

2.2 Pharmacy claims: New Hampshire Comprehensive Health Care Information System (NHCHIS)

The main objective of the empirical analysis is to determine the effect of pediatric labeling changes on drug utilization. To that end, we obtained pharmacy claims from New Hampshire’s all-payer claims database – the New Hampshire Comprehensive Health Care Information System (NHCHIS) – from 2007 to 2013. The NHCHIS data contains insurance claims for most privately insured residents of New Hampshire. For pediatric patients, the primary omission from the data is thus Medicaid. Since Medicaid provides insurance to millions of US children, the fact that the data does not include Medicaid is an unfortunate but unavoidable limitation. For adults, the primary omission is Medicare. Crucially, in addition to the drug and the year during which the prescription was filled, each pharmacy claim in the data contains the age of the patient. We utilize the NHCHIS data because it is publicly available, contains an age variable, and is based upon a sufficiently large sample to measure pediatric drug utilization.

One limitation of the NHCHIS data is that we do not observe the reason that each drug was prescribed. We must therefore combine all of the prescriptions for a drug together, irrespective of the underlying condition being treated. Labeling changes do not always apply to all of the conditions that a drug treats, so in those cases our measure of utilization will be broader than the specific conditions described in the label.

2.3 Combined dataset

We combine the pediatric labeling data with the NHCHIS data by drug and patient age. The age variable allows us to identify the relevant pediatric ages for each labeling change, and to compare utilization trends for those ages to adult ages unaffected by the labeling change.

We restrict the sample of labeling changes to those occurring between 2009 and 2011, so that we have at least two full years of utilization data both prior to and after all labeling changes. The FDA pediatric labeling data contains labeling changes for 98 distinct drugs over the 2009 to 2011 period.⁸ We impose several additional sampling restrictions. First, we exclude 24 drugs for which the pediatric labeling information was added concurrent to the drug’s approval (because in these cases there is no pre period). Second, we exclude 38 drugs

⁸For the handful of drugs with multiple labeling changes during the sample period, we identify any pediatric ages that were affected by only one labeling change during the period, excluding ages potentially affected by multiple changes.

for which there is a negligible quantity of prescriptions (either pediatric, adult, or both) in the NHCHIS data. For instance, the drug Suprane, which is an anesthetic used during surgery, does not appear at all in the pharmacy claims data. Third, we exclude 3 drugs for which the labeling change did not clearly represent either positive or negative news in terms of pediatric use. Two of these labeling changes added general information about biologic use, while the third added information about maximum daily dosing.

After performing the sample restrictions, the final sample contains 33 drugs. The full list of these drugs is given in Table 7 in the appendix, including the specific pediatric ages to which each labeling change applied. 20 drugs have positive labeling changes, 11 drugs have negative labeling changes, and 2 drugs have both. For the drugs with both positive and negative labeling changes, the change is positive for some ages and negative for other ages. Given the relatively small sample size, we pool together all labeling changes irrespective of whether the FDA attributed the changes to BPCA, PREA, or both.⁹

For each drug that experienced a pediatric labeling change, our primary dependent variable is that drug’s market share (by age and year).¹⁰ We define markets drug-by-drug by researching drugs that treat the same condition(s) specified by the labeling change. The primary source of this research is medical websites such as the Mayo Clinic and WebMD. We define markets narrowly, so that they include drugs that treat the same condition and that share some chemical similarities. Take the drug Protonix, for instance, which treats gastroesophageal reflux disease. There are two main classes of drugs that treat gastroesophageal reflux disease: proton pump inhibitors and H2 blockers, which work via different mechanisms. Protonix is a proton pump inhibitor, so we define the market for Protonix to be proton pump inhibitors (excluding H2 blockers). In Section 4, we confirm that the results are robust to defining markets using a broader drug classification system that was constructed by the federal government.

For each drug, we define the treatment group as the set of pediatric ages specified by the labeling change. For example, if a pediatric labeling change establishes safety and efficacy for patients aged 12 to 17, then we define the treatment group for that drug to be patients

⁹In the final sample, there are 9 drugs whose labeling changes were attributed to BPCA, 12 to PREA, and 12 to both. Drugs under PREA enter the sample since the FDA often approves drugs for adult use while allowing manufacturers additional time to complete pediatric trials (GAO (2011)). Drugs can fall under both PREA and BPCA when manufacturers performed clinical trials beyond the requirements of PREA, such as testing indications relevant to pediatric populations but which are not approved in adults (GAO (2011)).

¹⁰To explore whether pediatric labeling changes result in market expansion/contraction – as opposed to only shifting shares – we have also estimated models with market size as the dependent variable. The estimated effects of pediatric labeling changes on market size are not statistically significant either for positive labeling changes or negative labeling changes.

Table 1: In-Sample Prescription Counts and Shares

	Across in-sample drugs:	
	Mean	Median
<i>Per year average (2007-2013):</i>		
Pediatric Prescriptions (affected ages)	6,913	1,719
Adult Prescriptions (21-39)	25,308	19,146
<i>In years prior to the labeling change:</i>		
Pediatric Share (affected ages)	0.229	0.109
Adult Share (21-39)	0.243	0.140

aged 12 to 17. We define the control group for all drugs to be adults aged 21 to 39.¹¹ We eliminate older adults, as their utilization trends are arguably less likely to represent a reasonable counterfactual for the affected pediatric ages. We discard all pediatric ages that were not explicitly affected by the labeling change and adults aged 18 to 20 because these individuals do not cleanly fit into either the treatment or control group. For instance, a doctor may be more comfortable prescribing a medication to an 18-year-old following clinical trials demonstrating efficacy for 17-year-olds.

In Section 4, we confirm that the results are robust to using alternative adult control ages. In the appendix (Section 7.2), we present results from a model that defines the pediatric ages not explicitly mentioned in the labeling change as a separate treatment group. For example, if a pediatric labeling change establishes safety and efficacy for patients aged 12 to 17, this model considers patients aged 0 to 11 as a separate treatment group. We find small and statistically insignificant effects of labeling changes for the pediatric ages not explicitly covered by the labeling change.

For the drugs in our final sample, Table 1 presents average yearly prescription counts for the affected pediatric ages and adults aged 21 to 39, along with information about shares prior to the labeling changes under examination. On average, the NHCHIS data contains more than 30,000 prescriptions for each drug/market in our final sample (per year): 6,913 for the affected pediatric ages and 25,308 for adults aged 21 to 39. The median yearly

¹¹An implicit assumption of this approach is that pediatric labeling changes do not affect adult utilization. This assumption would be violated if, for instance, safety concerns from pediatric clinical trials spill over to adults (see, e.g., Busch and Barry (2009)). To support the assumption that adults are largely unaffected in our sample, we have estimated models that compare adult market shares before and after pediatric labeling changes. We estimate small and statistically insignificant effects. We have also estimated our difference-in-differences models excluding negative labeling changes affecting adolescents, as such changes may be more likely to spill over to adults. The estimates are essentially unchanged.

prescription counts are somewhat smaller than the averages, but still large: 1,719 for the affected pediatric ages and 19,146 for adults aged 21 to 39. On average, drugs with labeling changes account for roughly 20 percent of the prescriptions in each market. Pediatric and adult shares are similar, although there is heterogeneity across drugs. In particular, drugs with subsequent positive (negative) labeling changes have larger (smaller) pediatric shares than adult shares *prior to the labeling changes*. We discuss this point in more detail in the context of the empirical results in Section 3.3.

3 Empirical Analysis

3.1 Preview of the identification strategy

To illustrate our approach for measuring the impact of pediatric labeling changes on utilization, consider Axert, a triptan migraine drug. Axert was approved by the FDA in 2001 for use in adults. To adhere to PREA requirements, the manufacturer of Axert, Janssen Pharmaceuticals, then performed pediatric clinical trials in patients aged 12 to 17. Janssen submitted the results of these trials to the FDA in October 2008, and in April 2009 the FDA expanded Axert’s approved indications to cover adolescents aged 12 to 17. Figure 3 displays the change in the “indications and usage” section of the label.

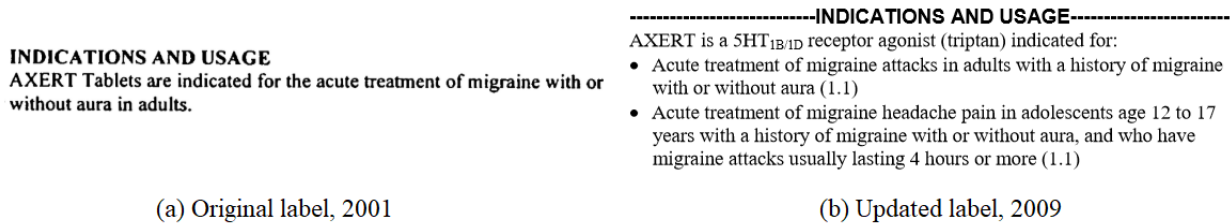


Figure 3: Axert Labels Before and After Pediatric Labeling

We calculate Axert’s share among triptan migraine drugs for both the treatment group (ages 12 to 17, as specified by the labeling change) and the control group (ages 21 to 39). Figure 4 plots changes in Axert’s share of prescriptions relative to the year prior to the labeling change (2008). Adult and pediatric share trends remain similar up through the year of the labeling change, and the adult share shows no break from trend following the labeling change. By contrast, the share for the affected pediatric ages increases by over three percentage points in the years following the labeling change. The magnitude of any divergence in these trends identifies the impact of labeling changes on pediatric utilization.



Figure 4: Adult and Pediatric Axert Utilization Patterns

3.2 Regression specification

The main regression specification is a fixed effects model of the form:

$$share_{ajdt} = \alpha_{jd} + \gamma_{dt} + \beta_1 \cdot positive_{jdt} + \beta_2 \cdot negative_{jdt} + \varepsilon_{ajdt}, \quad (1)$$

where $share_{ajdt}$ is drug d 's share of prescriptions for patients of age a (in age group j : treatment or control) and year t . We construct the dependent variable $share_{ajdt}$ from the prescription claims data as an average of the binary outcome of whether the patient filled a prescription for drug d or a different drug in the same market. α_{jd} are drug-age group fixed effects and γ_{dt} are drug-year fixed effects. $positive_{jdt}$ is an indicator variable that equals one for the affected ages when a drug experiences a positive labeling change. $negative_{jdt}$ is an analogous indicator variable that equals one for the affected ages when a drug experiences a negative labeling change. In the year of the labeling change, we set $positive_{jdt}$ and $negative_{jdt}$ to be the fraction of months in the year for which the labeling change was in effect. For instance, if a positive labeling change for a drug occurred in December 2010, $positive_{jdt}$ would be coded as 1/12 in 2010 and 1 thereafter for the affected ages.

With this specification, identification of the effect of labeling changes on utilization closely follows the logic described in Section 3.1. The drug-year fixed effects allow the adult share to vary flexibly across drugs and years. The drug-age group fixed effects allow a drug-specific

level shift in share for the affected pediatric ages compared to adults. The coefficients β_1 and β_2 measure the change in utilization after pediatric labeling changes for the affected pediatric ages compared to adults.

One key identifying assumption is that – if not for the labeling change – shares for the affected pediatric ages would have evolved in parallel to the observed changes for adults. As a suggestive test of this assumption, we estimate a more flexible version of equation (1) that compares share trends between the affected pediatric ages and adults both before and after labeling changes, commonly referred to as a “leads and lags” model:

$$share_{ajdt} = \alpha_{jd} + \gamma_{dt} + \sum_{k=-2}^2 \beta_1^k \cdot positive_{jdt}^k + \sum_{k=-2}^2 \beta_2^k \cdot negative_{jdt}^k + \varepsilon_{ajdt}. \quad (2)$$

$positive_{jdt}^k$ and $negative_{jdt}^k$ are indicator variables that equal one for the affected pediatric ages when a drug is k years away from a labeling change (to be clear, the k superscripts are *not* exponents). We examine share patterns two or more years prior to the labeling change ($k = -2$) up to two or more years after ($k = 2$). Since our data only spans 2007-2013 and the labeling changes occur between 2009-2011, we pool together all data two or more years away from the labeling change. Separately examining additional years would generate changes in the sample of drugs used to identify the coefficients. For instance, drugs with labeling changes in 2011 cannot inform estimates for three or more years after a labeling change, since 2014 is beyond the time period of the data.¹² To achieve identification, we constrain the coefficients for the year before the labeling change ($k = -1$) to be zero. The estimates for $k = -2$ capture any deviations in share patterns between the affected pediatric ages and adults prior to labeling changes, while the estimates for $k \geq 0$ capture the impact of labeling changes over time.

We estimate all specifications by weighted least squares, weighting each observation by the number of prescriptions over which the share is calculated. To allow for arbitrary correlation in the errors across ages and years within each drug, we cluster the standard errors by drug.

3.3 Main results

Figure 5 plots the estimates from the leads and lags model (equation (2)). Tabular results are reported in Table 8 (in the appendix). Prior to labeling changes, shares evolve similarly for the affected pediatric ages and adults, as evidenced by the small and insignificant estimate

¹²Despite this limitation, we have also estimated models including one additional lead year ($k = -3$) and one additional lag year ($k = 3$). There is no substantial difference in the results.

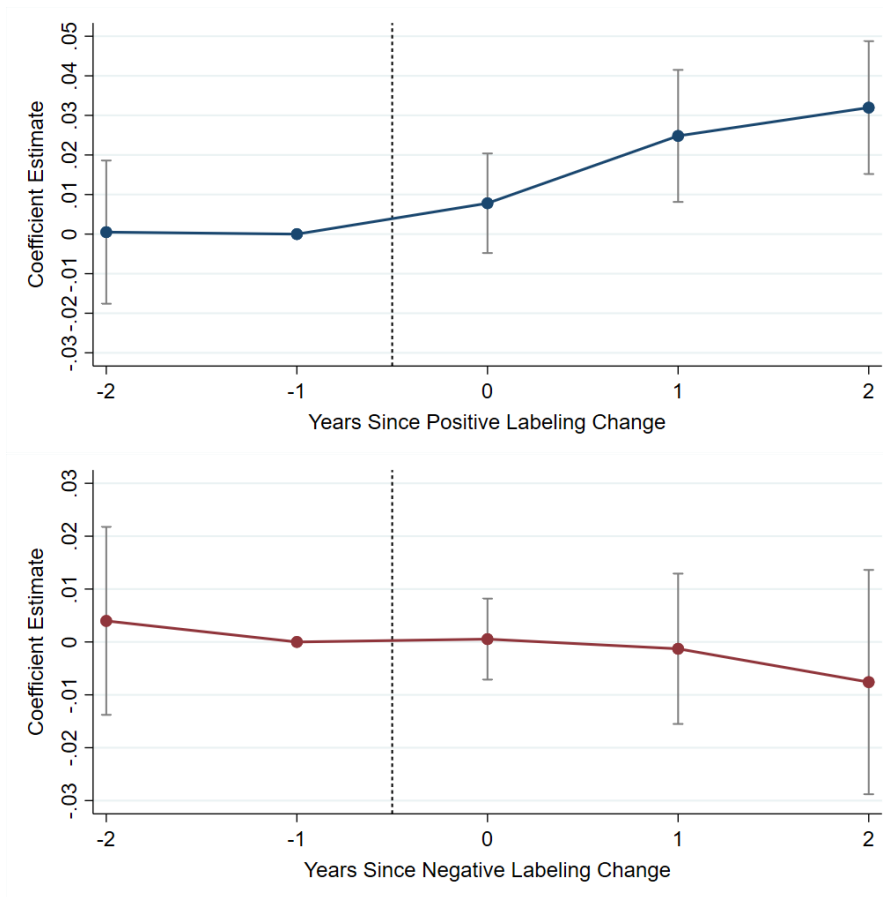


Figure 5: Leads and Lags Coefficient Estimates The top panel reports estimates for positive labeling changes and the bottom panel reports estimates for negative labeling changes. Vertical bars denote 95 percent confidence intervals. The year before the labeling change ($k = -1$) is the omitted category.

for $k = -2$. For positive labeling changes, shares for the affected pediatric ages increase by nearly one percentage point in the year of the labeling change. In subsequent years, shares for the affected pediatric ages continue to increase relative to adult shares: the point estimates indicate two to three percentage point increases and the estimates are statistically significant at the 1 percent level. For negative labeling changes, the point estimate for two or more years following the labeling change suggests a (statistically insignificant) decrease in share of 0.8 percentage points.

Table 2 presents the results from the pre-post specification (equation (1)). For our preferred specification (column (1)), positive labeling changes lead to a 2.8 percentage point increase in pediatric share (on average). Given average baseline shares of 22.9 percent (Table 1), this result corresponds to a 12 percent increase in share. The point estimate for negative labeling changes indicates a 0.9 percentage point decrease in pediatric share, although the

Table 2: The Effect of Pediatric Labeling Changes on Utilization

	(1)	(2)	(3)	(4)
	Main	Drop year of change	log(share)	log(share), drop <1%
Post Positive Labeling Change	0.028*** (0.010)	0.030** (0.011)	0.091* (0.051)	0.118*** (0.041)
Post Negative Labeling Change	-0.009 (0.010)	-0.008 (0.011)	0.062 (0.101)	-0.006 (0.065)
Observations	6,355	6,094	5,340	4,745
R-squared	0.935	0.936	0.930	0.920
$H_0: \beta_1 = \beta_2$	0.006***	0.012**	0.800	0.087*
$H_0: \beta_1 = -\beta_2$	0.216	0.198	0.185	0.187

Notes: *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$. Standard errors are clustered by drug and observations are weighted by total prescriptions. All specifications include drug-age group and drug-year fixed effects. The bottom two rows of the table report the p-values of (i) a test of the null hypothesis that positive and negative labeling changes have the same effect ($\beta_1 = \beta_2$) and (ii) a test of the null hypothesis that positive and negative labeling changes have opposite-signed effects of the same magnitude ($\beta_1 = -\beta_2$).

estimate is not statistically significant. The remaining columns of the table present results from slightly modified specifications, with the results broadly consistent with our preferred specification. In column (2), we drop the year of the labeling change: the estimates are essentially unchanged. In column (3), we estimate the model with the natural logarithm of share as the dependent variable so that the coefficients reflect percent changes. Positive labeling changes are estimated to increase shares by about 9 percent. The point estimate for negative labeling changes is positive (surprisingly), but the standard error is extremely large. In column (4), we estimate the model suppressing shares less than one percent, because some observations have very small share values (which are particularly influential on a log scale). Positive labeling changes are estimated to increase shares by about 12 percent, while the estimate for negative labeling changes shrinks to near zero.¹³

On balance, the results indicate positive and statistically significant effects of positive labeling changes of around 3 percentage points (or 9 to 12 percent). For negative labeling changes, we fail to reject the null hypothesis of no effect at conventional significance levels. We can reject the null hypothesis that positive and negative labeling changes have the same effect for most specifications. If uncertainty about a drug's safety and efficacy was entirely

¹³The results are similar using an alternative approach that drops drugs for which 75 percent or more of a drug's pediatric and/or adult observations have a share of less than 1 percent. With that alternative approach, the coefficient on positive labeling changes is 0.122 (with a p-value of 0.025) and the coefficient on negative labeling changes is -0.005 (with a p-value of 0.898).

symmetric, we would anticipate that positive and negative labeling changes would lead to utilization responses that are of the opposite sign, but the same magnitude. We are unable to reject this null hypothesis for any of the four specifications.

3.4 Discussion of mechanisms

Marketing

One natural question is to what extent the observed utilization response might be driven by increased marketing by drug manufacturers. Since it is illegal for manufacturers to promote off-label uses of their products, positive labeling changes may permit marketing that was otherwise not possible. The literatures examining pharmaceutical detailing (see, e.g., Mizik and Jacobson (2004); Larkin et al. (2017); Shapiro (2017)) and direct-to-consumer advertising (see, e.g., Wosinska (2002); Iizuka and Jin (2005); Sinkinson and Starc (2017)) suggest that both can meaningfully affect physician and patient behavior. Given the relatively small size of the pediatric population compared to adults – see Section 5.2 for more details – we suspect that changes in marketing following pediatric labeling are not substantial. Nonetheless, it is certainly possible that at least part of the observed utilization response reflects changes in marketing, but we view direct examination of that possibility to be beyond the scope of the present paper.

There is also a sense in which our estimates are conservative if they partially include the effect of changes in marketing. In Section 5.2, our back-of-the-envelope calculations suggest that the value of pediatric prescriptions shifted by labeling changes often needs to be very large (hundreds of dollars per prescription) in order to outweigh the costs of pediatric exclusivity. If our utilization estimates capture both the effect of labeling changes and increases in marketing, the standalone effect of positive labeling changes is likely smaller than what we estimate. Therefore, the value of pediatric prescriptions shifted by labeling changes would need to be *even larger* than what we report in Section 5.2.

Pricing

Besides physician and patient responses to updated labeling, changes in utilization could also potentially be driven by changes in drug pricing and/or insurance generosity. To explore this possibility, we have also estimated models with drug prices and consumer out-of-pocket spending as dependent variables. Since these outcomes are not expected to vary by the age of the patient, we do not compare pediatric and adult patients in these models (in contrast

to the main difference-in-differences analysis). Instead, we compare outcomes for drugs with labeling changes to (i) outcomes for competing drugs and (ii) outcomes for the same drugs prior to the labeling changes. For both comparisons, we do not detect statistically significant evidence that the utilization effects might be driven by changes in pricing and/or insurance generosity.

Learning

One possibility for the arguably small utilization responses is learning by physicians (patients, and/or insurers) about the safety and efficacy of drugs in pediatric patients several years prior to labeling changes. In that case, the labeling change itself will likely have less of an impact on pediatric utilization, as much has already been learned via clinical experience. Our results are consistent with this possibility. Specifically, the estimates of the drug-age group fixed effects from equation (1) indicate that – *prior to labeling changes* – pediatric shares are larger than adult shares for drugs with subsequent positive labeling changes and smaller than adult shares for drugs with subsequent negative labeling changes. On average, pediatric shares are 2.2 percentage points higher than adult shares for drugs with subsequent positive labeling changes and 7.8 percentage points lower than adult shares for drugs with subsequent negative labeling changes. These differences are statistically distinguishable both from zero and from each other (at the 1 percent level).

3.5 Heterogeneity based on pediatric novelty

We now examine whether the utilization response is larger for the *first* drug in a market with a positive labeling change. When other drugs in the market have already been demonstrated to be safe and effective in children, on the other hand, the utilization response might be more muted. If utilization is indeed more responsive to the first instance of positive pediatric labeling, then policymakers might want to consider providing correspondingly stronger rewards to manufacturers for generating that information (similar to the way that the FDA expedites approval for breakthrough drugs).¹⁴

Of the 22 drugs in the final sample with a positive labeling change, 7 were the first drugs in their respective markets to have a positive labeling change for similar pediatric ages and 15

¹⁴We do not examine negative labeling changes in an analogous way because (i) the sample size is half as large and (ii) it is less clear how to split the sample. For example, one could imagine different effects for drugs that were the first in the market to be tested, those where other drugs in the market also have negative pediatric results, those where at least one other drug has positive pediatric results, etc.

Table 3: Effect Heterogeneity by Pediatric Novelty

	(1)	(2)	(3)	(4)
	Main	Drop year of change	log(share)	log(share), drop <1%
Post Positive Labeling Change, First in Market	0.045 (0.027)	0.048* (0.026)	0.937** (0.381)	0.473** (0.220)
Post Positive Labeling Change, Not First in Market	0.027** (0.010)	0.029** (0.012)	0.055 (0.048)	0.103** (0.043)
Observations	3,983	3,842	3,519	3,266
R-squared	0.943	0.944	0.931	0.926
H_0 : effects are equal	0.548	0.512	0.032**	0.115

Notes: *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$. Standard errors are clustered by drug and observations are weighted by total prescriptions. All specifications include drug-age group and drug-year fixed effects. The bottom row of the table reports the p-value of a test of the null hypothesis that there is no heterogeneity in effects.

were not (based on the FDA labeling change data). To test whether the utilization response is different between these two groups, we estimated models like equation (1) but allowing the treatment effect to vary by whether or not the drug was the first drug in its market with a positive labeling change.

Table 3 reports the results. In columns (1) and (2), the estimated effect of positive labeling changes on share is more than 60 percent larger for first-in-market positive labeling changes than not-first-in-market positive labeling changes, but the standard error is also much larger. In both cases, we are unable to reject the null hypothesis of no difference in effects. In columns (3) and (4), the coefficient estimates for first-in-market positive labeling changes increase considerably. The estimate of 0.473 in the final column, for instance, implies that a first-in-market drug with a positive labeling change experiences a share increase of 60.5 percent ($=\exp(0.473)-1$). In column (3), we can reject the null hypothesis of equal effects at the 5 percent level. In column (4), we narrowly fail to reject the null hypothesis of equal effects at the 10 percent level.

On balance, these results suggest that if a drug is novel in demonstrating safety and efficacy in children, it can reasonably expect a larger utilization response than if competing drugs had similarly positive pediatric clinical trial results. That said, we have limited power to examine potential sources of heterogeneity in effects across our sample of 33 drugs, especially because labeling changes differ – in difficult to codify ways – in how much “news” they contain. As a result, it is unsurprising that these estimates are quite noisy.

4 Robustness Checks

We now turn to robustness checks of the main analysis.

4.1 Alternative market definition

First, we confirm that the results are robust to using an alternative market definition. To do so, we re-estimate equation (1) using the market definition contained in the Department of Veterans Affairs *National Drug File*, which splits drugs into more than 500 distinct categories. This market definition is contained in other sources as well: for instance, the Centers for Medicare & Medicaid Services include the same market definition in their prescription drug files. The alternative market definition tends to be somewhat larger than the definition we use in the main analysis: e.g., “antivirals” are a single category in the National Drug File, whereas our preferred market definition would split antivirals based on the specific viral infection treated by a drug. The results are reported in Table 4. The effect of positive labeling changes remains positive and statistically significant, whereas we cannot reject the null hypothesis of no effect for negative labeling changes.

Table 4: Alternative Market Definition

	(1)	(2)	(3)	(4)
	Main	Drop year of change	log(share)	log(share), drop <1%
Post Positive Labeling Change	0.027* (0.015)	0.031* (0.016)	0.103 (0.062)	0.119** (0.053)
Post Negative Labeling Change	-0.005 (0.013)	-0.005 (0.014)	0.172 (0.160)	-0.048 (0.138)
Observations	6,417	6,152	5,340	4,624
R-squared	0.932	0.934	0.919	0.926
$H_0: \beta_1 = \beta_2$	0.093*	0.098*	0.696	0.219
$H_0: \beta_1 = -\beta_2$	0.282	0.259	0.112	0.663

Notes: ***p<0.01, **p<0.05, *p<0.10. Standard errors are clustered by drug and observations are weighted by total prescriptions. All specifications include drug-age group and drug-year fixed effects. The bottom two rows of the table report the p-values of (i) a test of the null hypothesis that positive and negative labeling changes have the same effect ($\beta_1 = \beta_2$) and (ii) a test of the null hypothesis that positive and negative labeling changes have opposite-signed effects of the same magnitude ($\beta_1 = -\beta_2$).

4.2 Alternative control ages

Second, we confirm that the results are robust to defining the control group with different adult ages. In Table 5, we report results from 12 different control group age bands. For comparison purposes, the ages used for the main results in Table 2 (21 to 39) are reported in bold text. For all specifications, the estimated effect of positive labeling changes remains positive and statistically significant. For negative labeling changes, we continue to be unable to reject the null hypothesis of no effect, although the point estimate does become larger in magnitude for some specifications.

Table 5: Alternative Control Ages

	Control Group Ages					
	21-29	21-39	21-49	21-64	21+	31-39
Post Positive Labeling Change	0.029*** (0.009)	0.028*** (0.010)	0.024** (0.010)	0.023** (0.010)	0.023** (0.009)	0.027** (0.011)
Post Negative Labeling Change	-0.005 (0.012)	-0.009 (0.010)	-0.014 (0.011)	-0.018 (0.011)	-0.018 (0.011)	-0.006 (0.010)
$H_0: \beta_1 = \beta_2$	0.007***	0.006***	0.008***	0.010***	0.009***	0.018**
$H_0: \beta_1 = -\beta_2$	0.163	0.216	0.527	0.760	0.743	0.196
	31-49	31-64	31+	41-49	41-64	41+
Post Positive Labeling Change	0.023** (0.010)	0.022** (0.010)	0.022** (0.009)	0.019** (0.009)	0.019** (0.009)	0.019** (0.008)
Post Negative Labeling Change	-0.015 (0.012)	-0.018 (0.012)	-0.018 (0.012)	-0.016 (0.015)	-0.020 (0.014)	-0.019 (0.014)
$H_0: \beta_1 = \beta_2$	0.017**	0.016**	0.014**	0.047**	0.026**	0.023**
$H_0: \beta_1 = -\beta_2$	0.619	0.837	0.804	0.908	0.959	0.988

Notes: ***p<0.01, **p<0.05, *p<0.10. Standard errors are clustered by drug and observations are weighted by total prescriptions. All specifications include drug-age group and drug-year fixed effects. The bottom two rows of each panel report the p-values of (i) a test of the null hypothesis that positive and negative labeling changes have the same effect ($\beta_1 = \beta_2$) and (ii) a test of the null hypothesis that positive and negative labeling changes have opposite-signed effects of the same magnitude ($\beta_1 = -\beta_2$).

4.3 Leaving out drugs one-by-one

Third, we confirm that the results are robust to excluding drugs from the sample one at a time. Since the sample contains only 33 drugs in total, it is possible that the results are driven by a few pivotal drugs. To examine this possibility, we re-estimate equation (1) leaving out each drug one-by-one. Across these 33 specifications, the minimum estimated

effect of positive labeling changes is 1.9 percentage points and the maximum estimated effect is 3.1 percentage points, with both estimates significant at the 5 percent level. The minimum estimated effect of negative labeling changes is -1.3 percentage points and the maximum estimated effect is -0.05 percentage points, with neither estimate significant at the 10 percent level.

4.4 Alternative modeling approach: multinomial logit

Fourth, we confirm that the results are robust to an alternative modeling approach in which we estimate a multinomial logit discrete choice model (in place of the main analysis with market share as the dependent variable). To fix ideas, consider a single market (e.g., triptan migraine drugs). Denote the indirect utility of drug d in year t for each individual i requiring a prescription by:

$$U_{ijd} = \alpha_{jd} + \gamma_{dt} + \beta_1 \cdot \text{positive}_{jdt} + \beta_2 \cdot \text{negative}_{jdt} + \varepsilon_{ijd}, \quad (3)$$

where j denotes whether individual i 's age places them in the treatment or control group. This expression is analogous to the difference-in-differences formulation but with the left-hand-side of the equation being the indirect utility of a drug rather than its market share. Given the utility equation (3) and assuming that ε_{ijd} is iid type 1 extreme value, the ex-ante probability an individual i (in age group j) chooses drug d in year t is given by the logit formula:

$$P(i \text{ chooses } d | j, t) = \frac{\exp(\alpha_{jd} + \gamma_{dt} + \beta_1 \cdot \text{positive}_{jdt} + \beta_2 \cdot \text{negative}_{jdt})}{\sum_k \exp(\alpha_{jk} + \gamma_{kt} + \beta_1 \cdot \text{positive}_{jkt} + \beta_2 \cdot \text{negative}_{jkt})}, \quad (4)$$

where the sum in the denominator is over all drugs in the market.¹⁵ We assume that there is no outside option: i.e., that every consumer buys one of the drugs in the market.

After formulating these probabilities for all drugs and markets, we estimate the parameters of the model via maximum likelihood. As with the main difference-in-differences analysis, identification of the effects of labeling changes in the multinomial logit model rests on a parallel trends assumption. Whereas in the main analysis the identifying assumption is that the *market shares* for the affected pediatric ages would have evolved in parallel to the market shares for the adult control ages, here the identifying assumption is that the *indirect*

¹⁵One benefit of this approach is that multiple labeling changes among competing drugs are straightforwardly incorporated into the model. If one drug in a market experiences a labeling change, the market share of competing drugs will change in turn via the logit formula (equation (4)).

Table 6: Multinomial Logit Specification

	Coefficient Estimate	Change in Share	% Change in Share
Post Positive Labeling Change	0.350*** (0.073)	0.039*** (0.012)	29.0%*** (7.8%)
Post Negative Labeling Change	-0.020 (0.132)	-0.001 (0.008)	-1.9% (11.8%)

Notes: *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$. The specification includes drug-age group and drug-year fixed effects. The p-value of a test of the null hypothesis that positive and negative labeling changes have the same effect ($\beta_1 = \beta_2$) is 0.005. The p-value of a test of the null hypothesis that positive and negative labeling changes have opposite-signed effects of the same magnitude ($\beta_1 = -\beta_2$) is 0.048. The standard errors for the share changes are calculated via the bootstrap.

utility for the affected pediatric ages would have evolved in parallel to the indirect utility for the adult control ages.

Table 6 presents the coefficient estimates of β_1 and β_2 along with the implied effect on shares. As with the main difference-in-differences analysis, positive labeling changes are estimated to have a positive and statistically significant effect while the effect for negative labeling changes is small in magnitude and statistically indistinguishable from zero. To calculate the estimated effect on shares, we set *positive_{jdt}* and *negative_{jdt}* equal to zero in each case that they are equal to one and then re-compute shares according to the logit model. The numbers in the table are the resulting changes in shares averaged over all cases. For positive labeling changes, the estimated effect on shares is consistent with the main difference-in-differences estimates, although somewhat larger in magnitude. For negative labeling changes, the estimates are close to zero and statistically insignificant.

5 Policy Implications

The primary objective of the paper thus far has been to quantify changes in drug utilization following pediatric labeling changes. We now turn to the implications of the estimated magnitude of those changes for public policy. The calculations here are by necessity back-of-the-envelope. One immediate caveat is that our estimates are based purely on data from New Hampshire, which we then extrapolate to the national level. Instead of providing firm conclusions, the goal is to illustrate how the measured utilization responses can potentially help inform broader questions.

In Section 5.1, we examine manufacturer incentives to conduct pediatric clinical trials

in the absence of legislation like BPCA and PREA: is the estimated utilization response from positive labeling changes potentially enough to outweigh the cost of pediatric clinical trials? In Section 5.2, we assess the exclusivity provisions of BPCA: how much does the affected pediatric utilization from labeling changes need to be worth (in dollar terms) in order to outweigh the increased spending in the adult population due to extended market exclusivity?

5.1 Manufacturer incentives to conduct pediatric trials

To begin, we estimate the private returns to pediatric clinical trials – based in part on our estimates of the effect of labeling changes on utilization – and compare them to estimates of clinical trial costs from the literature. At first glance, this exercise may seem superfluous: given the history of pediatric labeling, manufacturers by and large did not conduct pediatric clinical trials prior to legislation like BPCA and PREA. Therefore, it stands to reason that the potential changes in utilization induced by positive pediatric clinical trial results are often not sufficient to outweigh the costs of clinical trials.

Nonetheless, there are at least two good reasons to examine the question directly. First, the results can confirm that our utilization estimates are reasonable: are the estimated magnitudes broadly consistent with the observed history of limited pediatric clinical data prior to BPCA and PREA? Second, it may be that the utilization changes induced by pediatric labeling changes are different now than they were several decades ago. Or, that the overall market size is larger and/or that prices are higher. If so, it could be that one of the main arguments for BPCA and PREA – that the market alone does not provide sufficient financial incentives for manufacturers to conduct pediatric trials – has meaningfully shifted.¹⁶

To start, consider the benchmark case where the manufacturer knows that a pediatric clinical trial will generate positive news about its drug. The gains to performing the trial in this case constitute an upper bound to the true gains, as in reality the trial may generate negative news. An estimate of the yearly revenue gain to a manufacturer from positive pediatric clinical trial results is given by:

$$\text{pediatric market size} \times \text{effect of a positive labeling change on share} \times \text{price},$$

¹⁶Similar arguments have recently been raised about Orphan Drug Incentives: e.g., “there are a number of examples of drugs approved solely for orphan indications that generate sales in excess of \$1 billion annually... [calling] into question the underlying premises of the incentives: that there is no viable commercial market to treat rare diseases.” Health Affairs Health Policy Brief: *Pricing Orphan Drugs*, July 2017. For academic research examining the impact of the Orphan Drug Act on innovation, see, e.g., Yin (2008) and Yin (2009).

where pediatric market size is the yearly total number of prescriptions filled for all drugs in the market.¹⁷ Since we do not have data on drug manufacturing costs, we limit our attention to revenues. Manufacturing costs are thought to be low for most drugs, so revenues arguably approximate profits. For each drug in our final sample, we estimate the market size by multiplying the observed number of prescriptions in New Hampshire (for the affected pediatric ages) by the ratio of (i) the US population under the age of 18 to (ii) the New Hampshire population under the age of 18 that is covered by private insurance, according to the American Community Survey. This adjustment scales up the observed pediatric prescriptions in New Hampshire to include both other states and other insurance types (Medicaid in particular).¹⁸ Based on the difference-in-differences analysis, the effect of a positive labeling change on a drug's share is 2.8 percentage points. Finally, we calculate the average price for each drug from the NHCHIS data (measured in 2013 dollars).¹⁹

Across the drugs in the final sample, the median estimated revenue benefit from a positive labeling change is \$3.8 million per year. That said, the distribution of estimates exhibits a tremendous amount of variation due to large differences in market sizes and prices. The 25th percentile estimate is \$0.7 million per year and the 75th percentile estimate is \$25.2 million per year. Depending on the drug and the years of patent protection remaining, drug manufacturers can thus potentially earn tens of millions of dollars from increased pediatric utilization following positive labeling changes.

How do these revenue estimates compare to the cost of pediatric clinical trials? Examining nine drugs that received pediatric exclusivity between 2002 and 2004, Li et al. (2007) estimate pediatric clinical trial costs ranging from \$6.3 million to \$59.6 million, with an average of \$24.2 million (in 2013 dollars).²⁰ Martin et al. (2017) report a median cost of \$21.4 million for phase III clinical trials. For the median drug in our final sample – for which we estimate a yearly revenue benefit of \$3.8 million from a positive labeling change – these clinical trial costs may easily be prohibitive, especially considering that about 20 percent of drugs are found to be unsafe and/or ineffective in pediatric patients (GAO (2011)). For drugs with

¹⁷An implicit assumption of this approach is that positive labeling changes do not expand the market. In models with market size as the dependent variable, we do not find clear evidence of changes in market size following labeling changes.

¹⁸According to the American Community Survey between 2008 and 2013, 0.277 percent of the US population under the age of 18 was privately insured in New Hampshire, yielding a multiplier of about $1/0.00277=361$.

¹⁹The prices we measure are gross of (unobserved) rebates from manufacturers to payers, and thus are likely greater than what manufacturers actually receive.

²⁰The estimates in Li et al. (2007) are in 2005 dollars (minimum \$5.3 million; maximum \$49.6 million; average \$20.2 million), which we convert to 2013 dollars using the CPI.

particularly high prices and/or pediatric demand, on the other hand, manufacturers may not need FDA incentives to perform pediatric clinical trials.

Overall, this result is consistent with the observed prevalence of pediatric labeling prior to BPCA and PREA, e.g. where 20 percent of new molecular entities approved in 1995 with a potential pediatric use included labeling information specific to pediatric patients (Wilson (1999)). For many drugs, it appears that pediatric clinical trial costs easily exceed the potential benefits, but for some drugs manufacturers would find it profitable to conduct pediatric trials even absent current legislation.

5.2 Pediatric exclusivity and consumer welfare

We now turn to the consumer welfare impact of pediatric exclusivity under BPCA. Before explaining the calculations, we provide an explanation of why pediatric exclusivity under BPCA might be welfare-enhancing even if manufacturers do not desire to perform the clinical trials without the incentives. Suppose temporarily that drug manufacturers were able to engage in perfect price discrimination and that patents lasted forever. Then, the expected social benefits of clinical trials would be equal to drug manufacturers' expected profits from performing those trials (because manufacturers can extract the full social benefits). As a result, there would be no room for government intervention to increase efficiency because drug manufacturers would perform clinical trials precisely in those cases in which the expected social benefits exceed the expected costs. In reality, however, the temporary nature of patent protection and the inability to perfectly price discriminate implies that drug manufacturers are unable to capture the full social value generated by clinical trials. As a result, drug manufacturers may have socially insufficient incentives to invest in clinical trials. The patent system is designed to balance the losses from underinvestment in research with the losses from temporary monopoly rights that patents create. For smaller markets, in which research is less likely without additional incentives, optimal patent policy (see, e.g., Nordhaus (1969)) suggests that manufacturers should receive stronger incentives. The exclusivity provisions of BPCA can be thought of as an attempt to provide those stronger incentives.

With these trade-offs in mind, we perform a back-of-the-envelope calculation to weigh the costs to consumers of extended exclusivity against the benefits of pediatric clinical trials. More specifically, the main cost of exclusivity is delayed generic competition leading to higher prices in the adult market, and the benefit of exclusivity is increased information about the drug's use in the pediatric population. To simplify the analysis, we assume that manufacturers would not find it profitable to conduct pediatric clinical trials absent the

exclusivity incentive, so that exclusivity is necessary to achieve the benefits of pediatric research. We also assume that the welfare benefit to pediatric research is limited to the aggregate utilization that is affected by the subsequent labeling change: i.e., there are no “peace of mind” benefits arising from increased knowledge about pediatric safety, benefits to potentially more accurate dosing, etc. beyond what is reflected in the utilization response.

The cost of exclusivity is six additional months of exclusivity for the drug (hereafter “monopoly”). Denote yearly monopoly spending in the adult population by S , the ratio of spending after generic entry to spending under monopoly by λ , and the years until patent expiration by τ . An estimate of the net present value of the cost of exclusivity is then:

$$\underbrace{\delta^\tau}_{\text{time discounting}} \cdot \underbrace{0.5 \cdot (1 - \lambda) \cdot S}_{\text{difference in spending between six months with and without generic competition}}, \quad (5)$$

where 0.5 reflects that the exclusivity provision lasts half a year.^{21,22} The cost of exclusivity increases with the level of monopoly spending S , the gap between monopoly spending and spending with generic competition $(1 - \lambda)$, and the discount factor δ , while decreasing in the years until patent expiration τ .

To quantify the benefit of exclusivity, denote the yearly quantity of prescriptions affected by the resulting pediatric labeling change by Δq . Further denote the average welfare benefit (in dollars) to each of these prescriptions by θ . This formulation of welfare benefits can be microfounded in a model in which, prior to labeling changes, utilization decisions are made on the basis of incomplete information about the drug, leading to inefficient consumption. See Figure 6 and the corresponding notes for a fuller explanation. Assuming that Δq is invariant across time and applies in perpetuity, an estimate of the net present value of the benefit of exclusivity, given discount factor δ , is then:

$$\sum_{t=0}^{\infty} \delta^t \cdot \theta \cdot \Delta q = \frac{\theta \cdot \Delta q}{1 - \delta}, \quad (6)$$

²¹This expression only includes additional spending in the adult population. Incorporating pediatric spending into the calculation is not straightforward because labeling changes could either increase or decrease pediatric spending, depending on the prices of the drugs being substituted to/away from. To simplify, we assume no impact on pediatric spending.

²²Consistent with the uptick in pediatric clinical trials post-BPCA, adding a term reflecting pediatric exclusivity to the calculations in Section 5.1 (a term like equation (5)) indicates that the financial benefits associated with extended exclusivity often outweigh the costs of pediatric clinical trials.

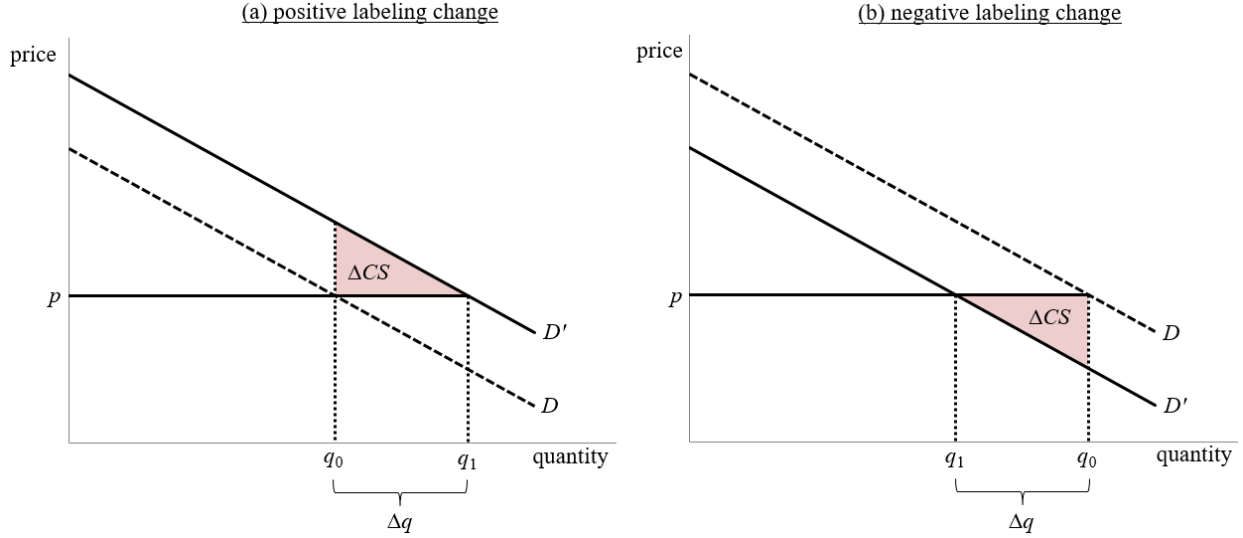


Figure 6: A Model of Labeling Changes and Consumer Welfare In both panels, D' represents the true value generated by a drug in the pediatric population. Prior to labeling changes, however, perceptions of the drug's value are either systematically below the true value (in the case of positive labeling changes) or above it (in the case of negative labeling changes). These mistaken perceptions are represented by the dashed demand curve D . Demand is determined by D prior to labeling changes (q_0) and D' after (q_1), whereas consumer surplus is always calculated according to D' . Price p is assumed invariant to labeling changes. Positive labeling changes correct misperceptions that caused underutilization, and negative labeling changes correct misperceptions that caused overutilization. In both cases, the increase in consumer surplus (ΔCS) is given by the shaded area. The increase in consumer surplus can equivalently be written as $\theta \cdot \Delta q$, where θ is the average difference between D' and p for the quantity affected by the labeling change.

where $t = 0$ is the year of the labeling change. The benefit increases with the quantity of shifted prescriptions Δq , the welfare benefit of each of these prescriptions θ , and the discount factor δ .

Setting the benefit greater than the cost and re-arranging, pediatric exclusivity is welfare-enhancing if:

$$\theta > \frac{(1 - \delta) \cdot \delta^\tau \cdot 0.5 \cdot (1 - \lambda) \cdot S}{\Delta q} \quad (7)$$

To get an idea of how much shifted prescriptions need to be worth for exclusivity to be welfare-enhancing, we calibrate the parameters on the right-hand-side of the inequality in (7) using our estimates as well as other outside sources. We set the social discount factor $\delta = 0.95$. For each drug in the sample, we set τ to be the years from the date of the labeling change until the date of patent expiration.²³ We set $\lambda = 0.3$, assuming that spending with

²³In cases where a drug is covered by multiple patents, there is some uncertainty about what the appropriate date of patent expiration is for the purpose of the calculation. We rely on industry reports that state the expected timing of generic entry.

generic competition is 30 percent of spending under monopoly.²⁴ We estimate the adult spending for each drug prior to patent expiration (S) using the NHCHIS data, scaled up to the national level.²⁵ Last, we estimate the quantity of prescriptions shifted by the labeling change (Δq) by multiplying the observed pediatric market size in the NHCHIS data by our estimate of the effect of labeling changes on shares, again scaled up to the national level.²⁶

For the median drug in our sample, the marginal pediatric patient's welfare benefit from a prescription (θ) must be at least \$646 (in 2013 dollars) to outweigh the increased spending in the adult population due to six months of additional exclusivity.²⁷ As with the first exercise, the distribution of estimates exhibits a lot of variation. The 25th percentile estimate is \$246 per prescription and the 75th percentile estimate is \$10,434 per prescription. The estimates as multiples of drug prices are also informative. For the median drug, each pediatric prescription shifted by the labeling change needs to be worth 3.5 times the drug's price for pediatric exclusivity to be welfare-enhancing. The 25th percentile estimate is 0.6 and the 75th percentile estimate is 34.1.

One of the main causes of these estimates approaching a thousand dollars or more is the often large differences in market size between the affected pediatric ages and the entirety of the adult population. For the median drug, there are 92 times as many prescriptions in the NHCHIS data for the adult population (21 and older) than the pediatric ages specified by the labeling change. The 25th percentile is 18 times and the 75th percentile is 732 times. To outweigh the six months of much higher spending in the adult population due to pediatric exclusivity, the value of the pediatric prescriptions affected by the labeling change thus needs to be quite large. To be clear, taking a stance on whether the value of increased pediatric information *does* arguably reach into the thousands of dollars is beyond the scope of this paper. That said, we do think it is worthwhile to roughly quantify what magnitudes are

²⁴Results from the literature often differ by the sample of drugs, number of generic entrants, and time since generic entry. For instance, Frank and Salkever (1997) find that generic prices are 50 percent of the brand's price at launch with 4 generic entrants and 30 percent with 12 or more generic entrants. Berndt and Aitken (2011) find that the average generic price relative to the brand price at the time of generic entry is 50 percent one year after generic entry and 23 percent two years after generic entry. We chose $\lambda = 0.3$ to be close to the middle of these estimates from the literature.

²⁵As with the pediatric population, this scaling is calculated using the American Community Survey. According to that data, 0.337 percent of US adults are privately insured in New Hampshire, yielding a multiplier of about $1/0.00337=296$.

²⁶For simplicity, we generate a common estimate for both positive and negative labeling changes by imposing that they have opposite-signed effects of the same magnitude and then re-estimating equation (1). The resulting estimate indicates a 2.0 percentage point effect of labeling changes (statistically significant at the 1 percent level).

²⁷For this analysis, we restrict the calculations to the 21 drugs in the final sample whose labeling changes the FDA attributed at least partially to BPCA.

necessary to outweigh the costs of extended exclusivity in the adult population.

It is also worth pointing out cases where pediatric exclusivity is more or less likely to be welfare-enhancing. Olson and Yin (2017) make several similar arguments in their work examining the FDA's decisions to issue written requests and manufacturer decisions to accept or decline them. First, while S and Δq will in general be positively correlated – the more prevalent a condition, the higher the spending and the more potential prescriptions to be shifted – in some cases these two parameters will move quite independently of one another. For instance, drugs with large adult populations but small pediatric populations will require a large θ in order to be welfare-enhancing. When deciding on which drugs to issue written requests under BPCA, the FDA might therefore want to consider the relative sizes of the adult and pediatric populations (if they do not do so already). In addition, it is clear that the benefit of pediatric exclusivity to manufacturers increases with the size of the adult population. While making the length of pediatric exclusivity dependent on the size of the adult population would likely require legislative action, the FDA does have discretion in specifying the type of pediatric study needed to fulfill a written request. For example, if a drug has a particularly large adult population, the FDA might consider requesting more demanding pediatric studies (e.g., larger sample sizes, more detailed and/or longer clinical endpoints, etc.), as the increased costs of such studies can be offset by the benefits of additional exclusivity in the large adult population.

Second, the earlier that a labeling change occurs in a drug's life cycle (i.e., a larger τ), the bigger the net benefit of exclusivity, as prescriptions start being shifted immediately while the cost of exclusivity is pushed into the future. However, Olson and Yin (2017) find that manufacturers tend to prioritize pediatric studies for drugs with less remaining patent life. There are several possible reasons for this divergence between social and private incentives. One reason is simply the time value of money: the exclusivity benefit of pediatric trials occurs only upon patent expiration, so manufacturers may prefer to incur the costs of pediatric trials as late as possible. Another similar reason is uncertainty surrounding the commercial longevity of a drug. For instance, if a manufacturer conducts pediatric trials early in a drug's life-cycle and then a next-generation product is developed that makes the drug obsolete, the manufacturer's pediatric exclusivity loses its value. Given the divergence between social and private incentives concerning the timing of pediatric clinical trials, the FDA may therefore want to consider taking time until patent expiration into account when issuing written requests and also constraining the timeframe for conducting the trials (if they do not do so already).

6 Conclusion

In this paper, we examine the effect of legislatively induced pediatric labeling changes on pediatric drug utilization using New Hampshire’s all-payer claims database. To separate the effect of labeling changes from other temporal factors affecting utilization, we exploit the fact that the labeling changes are specific to the pediatric population. On average, positive labeling changes disclosing that a drug is safe and effective increase the drug’s market share by (a statistically significant) 2.8 percentage points. Negative labeling changes disclosing that a drug is either unsafe or ineffective decrease the drug’s market share by (a statistically insignificant) 0.9 percentage points.

The results also suggest that physicians and patients may already know some of the information contained in labeling changes. In particular, pediatric shares are 2.2 percentage points higher than adult shares for drugs with subsequent positive pediatric labeling changes and 7.8 percentage points lower than adult shares for drugs with subsequent negative pediatric labeling changes. We also find suggestive evidence that pediatric utilization is more sensitive in cases in which a drug is the first in its market to be approved for pediatric use.

We conclude by examining the public and private benefits from pediatric clinical trials in light of the utilization estimates. The results are consistent with the observation that markets do not provide manufacturers with sufficiently strong incentives to perform pediatric clinical trials for many drugs, as the cost of clinical trials can easily dwarf the increased profits resulting from higher utilization. Turning to the welfare impact of pediatric exclusivity, we estimate – for the median drug – that the welfare benefit for the marginal pediatric patient must exceed the drug’s price by a factor of 3.5 for pediatric exclusivity to be welfare-enhancing. The 25th percentile estimate is 0.6 and the 75th percentile estimate is 34.1. This wide range of estimates indicates that there may be substantial value in the FDA exercising further discretion when issuing written requests.

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7 Appendix

7.1 Additional tables

Table 7: List of In-Sample Drugs

Brand Name	Manufacturer	Molecule(s)	Market Definition	Date of Labeling Change	Affected Ages
Lexapro	Forest Laboratories	Escitalopram	SSRI Antidepressants	3/19/2009	≤11, 12-17
Creon	Solvay Pharmaceuticals	Pancrelipase	Pancreatic Enzyme Products	4/30/2009	1-17
Axert	Janssen Pharmaceuticals	Almotriptan	Triptan Migraine Drugs	4/30/2009	12-17
Lamictal	GlaxoSmithKline	Lamotrigine	Anti-Epileptic Drugs	5/8/2009	≤2
Xyzal	UCB	Levocetirizine	Second-generation Antihistamines	8/21/2009	2-5
Valcyte	Genentech	Valganciclovir	Cytomegalovirus Drugs	8/28/2009	≤16
Welchol	Daiichi Sankyo	Colesevelam	Bile Acid Sequestrants	10/2/2009	10-17
Crestor	AstraZeneca	Rosuvastatin	Statins	10/15/2009	10-17
Protonix	Pfizer	Pantoprazole	Proton Pump Inhibitors	11/12/2009	0, 5-17
Abilify	Bristol-Myers Squibb	Aripiprazole	Antipsychotics	11/19/2009	6-17
Patanase	Novartis	Olopatadine	Intranasal Antihistamines	12/1/2009	6-11
Seroquel	AstraZeneca	Quetiapine	Antipsychotics	12/2/2009	13-17
Zyprexa	Eli Lilly	Olanzapine	Antipsychotics	12/4/2009	13-17
Daytrana	Noven Pharmaceuticals	Methylphenidate	Long-Acting ADHD Stimulants	12/14/2009	≤12
Flomax	Boehringer Ingelheim	Tamsulosin	Alpha-1-Adrenergic Receptor Antagonists	12/22/2009	2-16
Topamax	Janssen Pharmaceuticals	Topiramate	Anticonvulsants	12/22/2009	≤1
Tamiflu	Roche	Oseltamivir	Influenza Antiviral Drugs	2/22/2010	1-12
Differin	Galderma Laboratories	Adapalene	Topical Retinoids	3/17/2010	12-17
Omnaris	Takeda Pharmaceuticals	Ciclesonide	Nasal Corticosteroids	5/7/2010	≤11
Zylet	Bausch + Lomb	Loteprednol/Tobramycin	Ophthalmic Steroids with Anti-Infectives	6/3/2010	≤6
Serevent	GlaxoSmithKline	Salmeterol	Asthma Drugs	6/25/2010	≤17
Augmentin XR	Dr. Reddy's Laboratories	Amoxicillin/Clavulanate	Penicillin Antibiotics	8/27/2010	12-15
Vyvanse	Shire	Lisdexamfetamine	ADHD Stimulants	11/10/2010	13-17
Nasonex	Merck	Mometasone	Nasal Corticosteroids	1/19/2011	≤17
Invega	Janssen Pharmaceuticals	Paliperidone	Antipsychotics	4/6/2011	12-17
Kytril	Roche	Granisetron	Postoperative Nausea and Vomiting Drugs	4/29/2011	≤17
Plavix	Bristol-Myers Squibb	Clopidogrel	Antiplatelet Drugs	5/6/2011	≤12
Zenpep	Eurand Pharmaceuticals	Pancrelipase	Pancreatic Enzyme Products	6/15/2011	0
Truvada	Gilead Sciences	Emtricitabine/Tenofovir	Nucleoside Reverse Transcriptase Inhibitors	7/8/2011	12-17
Chantix	Pfizer	Varenicline	Smoking Cessation Aids	11/9/2011	≤17
Nexium	AstraZeneca	Esomeprazole	Proton Pump Inhibitors	12/15/2011	0
Maxalt	Merck	Rizatriptan	Triptan Migraine Drugs	12/16/2011	6-17
Keppra	UCB	Levetiracetam	Anti-Epileptic Drugs	12/16/2011	≤3

Table 8: Leads and Lags Coefficient Estimates

	Positive Labeling Change	Negative Labeling Change
Two or more years before	0.000 (0.009)	0.004 (0.009)
One year before	0 –	0 –
Year of labeling change	0.008 (0.006)	0.001 (0.004)
One year after	0.025*** (0.009)	-0.001 (0.007)
Two or more years after	0.032*** (0.009)	-0.008 (0.011)
Observations	6,355	
R-squared	0.935	

Notes: *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$. Standard errors are clustered by drug and observations are weighted by total prescriptions. The specification includes drug-age group and drug-year fixed effects.

7.2 Pediatric ages excluded from labeling changes

As shown in Table 7, many pediatric labeling changes specify a subset of the full pediatric population. For example, the pediatric labeling for the drug Axert only specified patients aged 12 to 17. In the results in the main text, we exclude the pediatric ages not explicitly mentioned in the labeling change because they do not cleanly fit into either the treatment or control group. Here, we include those ages as a separate treatment group and estimate a model similar to equation (1) but with two pediatric treatment effects: one for the affected ages specified in the labeling change (as in the main text) and another for the excluded ages not specified in the labeling change.

Table 9 reports the results. For both positive and negative labeling changes, the impact on utilization for the excluded pediatric ages is close to zero and statistically insignificant. For positive labeling changes, we are able to reject the null hypothesis that positive labeling changes have the same effect for the affected and excluded pediatric ages (at the 10 percent level).

Table 9: Effects for Excluded Pediatric Ages

	Coefficient Estimate
<i>Affected pediatric ages:</i>	
Post Positive Labeling Change	0.031*** (0.010)
Post Negative Labeling Change	-0.009 (0.010)
<i>Excluded pediatric ages:</i>	
Post Positive Labeling Change	0.007 (0.009)
Post Negative Labeling Change	0.001 (0.003)
Observations	8,010
R-squared	0.925
H_0 : affected=excluded (positive)	0.071*
H_0 : affected=excluded (negative)	0.235

Notes: *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$. Standard errors are clustered by drug and observations are weighted by total prescriptions. The specification includes drug-age group and drug-year fixed effects.

7.3 Adverse events

The FDA collects data on adverse events via the FDA Adverse Event Reporting System (FAERS).²⁸ Among other information, FAERS contains data on the drug(s) associated with each adverse event and the age of the patient. There are several limitations of the data. First, the FDA does not require that a causal link can be drawn between a drug and the adverse event. Therefore, reported adverse events are not necessarily due to the reported drug. Second, the data is based on self-reports, and thus does not capture the universe of adverse events. This second limitation makes it difficult to construct measures like the incidence of adverse events relative to a drug's overall utilization. That said, it is possible use the data to examine the frequency of reported adverse events and how that frequency varies across time and by patient age. Unfortunately, the reported quantity of adverse events for drugs in our final sample is extremely small. Between 2007 and 2013, the average number of reported pediatric adverse events per drug is 63 (less than 10 per year) and the median is 7 (1 per year). Therefore, there do not appear to be sufficient quantities in the FAERS data (for our sample) to examine the effect of pediatric labeling changes on adverse events.

²⁸<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>