Off-label Prescribing Among Office-Based Physicians

David C. Radley, MPH; Stan N. Finkelstein, MD; Randall S. Stafford, MD, PhD

Background: Unlike medicines prescribed for Food and Drug Administration–approved indications, off-label uses may lack rigorous scientific scrutiny. Despite concerns about patient safety and costs to the health care system, little is known about the frequency of off-label drug use or the degree of scientific evidence supporting this practice.

Methods: We used nationally representative data from the 2001 IMS Health National Disease and Therapeutic Index (NDTI) to define prescribing patterns by diagnosis for 160 commonly prescribed drugs. Each reported drug-diagnosis combination was identified as Food and Drug Administration–approved, off-label with strong scientific support, or off-label with limited or no scientific support. Outcome measures included (1) the proportion of uses that were off-label and (2) the proportion of off-label uses supported by strong scientific evidence. Multivariate analyses were used to identify drug-specific characteristics predictive of increased off-label use.

Results: In 2001, there were an estimated 150 million (95% confidence interval, 127-173 million) off-label mentions (21% of overall use) among the sampled medications. Off-label use was most common among cardiac medications (46%, excluding antihyperlipidemic and antihypertensive agents) and anticonvulsants (46%), whereas gabapentin (83%) and amitriptyline hydrochloride (81%) had the greatest proportion of off-label use among specific medications. Most off-label drug mentions (73%; 95% confidence interval, 61%-84%) had little or no scientific support. Although several functional classes were associated with increased off-label use ($P<.05$), few other drug characteristics predicted off-label prescription.

Conclusions: Off-label medication use is common in outpatient care, and most occurs without scientific support. Efforts should be made to scrutinize underevaluated off-label prescribing that compromises patient safety or represents wasteful medication use.

Arch Intern Med. 2006;166:1021-1026

Author Affiliations: Center for Evaluative Clinical Sciences, Dartmouth Medical School, Hanover, NH (Mr Radley); Program on the Pharmaceutical Industry, Sloan School of Management, Massachusetts Institute of Technology, Cambridge (Dr Finkelstein); and Program on Prevention Outcomes and Practices, Stanford Prevention Research Center, Stanford, Calif (Dr Stafford). Dr Finkelstein is now additionally with Harvard Medical School, Boston, Mass.

THE FOOD AND DRUG ADMINISTRATION (FDA) focuses on market entry for prescription drugs rather than regulating physicians' prescribing practices, allowing off-label use of medications for indications beyond those formally evaluated by the manufacturer. Off-label prescribing of medications is legal,[1] often thought to be supported by scientific evidence,[2] and common in certain clinical settings.[3,4] Although this practice provides a pathway to innovation in clinical practice, it raises key concerns about risks to patients and costs to the health care system.[5-7]

Despite sufficient evidence justifying some off-label practices, lack of FDA approval means that off-label uses are not given the same degree of scientific scrutiny as labeled indications. Scientific evidence documenting the efficacy of off-label uses in routine practice settings commonly falls short of what the drug's manufacturer would be required to provide the FDA to receive approval for that indication. Although regulation in this area is evolving, FDA policy prohibits direct-to-consumer promotion of drugs for unapproved uses and restricts such promotion to physicians.

Previously published studies of off-label prescribing typically consider this practice in the context of narrowly defined clinical populations, including those with psychiatric disorders,[3,8] those with human immunodeficiency virus and AIDS,[9] children,[10,11] pregnant women,[12] and others commonly underserved by FDA-approved medicines.[4,13] None of these studies have systematically described the overall magnitude of off-label prescribing or the consequences of prescribing drugs for unevaluated or underevaluated indications. A study published in 1985 examined the 100 most common uses of marketed medicines and found that 31 were for indications not initially approved by the FDA, of which 18 were not subsequently scrutinized.[14]

Using a nationally representative sample documenting physician prescribing by diagnosis, we examined the overall frequency and clinical circumstances of off-label prescription among commonly prescribed medications as a function of the strength of scientific support for those practices.

METHODS

We used a nationally representative survey of physician prescribing practices to examine off-label prescribing among office-based physicians in the United States. Observed drug uses were identified by clinical indication and determined to be labeled (FDA approved), off-label (lacking FDA approval) with scientific evidence of therapeutic efficacy, or off-label without supporting evidence. Our analytic goals were to estimate the magnitude of off-label use, the most frequent conditions and drug classes contributing to off-label use, and whether observed off-label uses were supported by scientific evidence and to identify medication-specific characteristics predictive of this practice.

DATA SOURCE

Data for this analysis come from the 2001 National Disease and Therapeutic Index (NDTI).[15] The NDTI is a continuing survey of US office-based physicians conducted by IMS Health (Plymouth Meeting, Pa). The NDTI contains nationally representative diagnostic and treatment data similar to that contained in the National Ambulatory Medical Care Survey.[16,17] A panel of office-based physicians is selected through random stratified sampling from the master lists of the American Medical Association and the American Osteopathic Association (both in Chicago, Ill) to participate in quarterly samplings of their clinical activity. Each quarter, approximately 3500 physicians report on each patient encounter during 2 randomly selected consecutive workdays. In 2001, there were 403 975 sampled patient-physician encounters with recorded medication therapy. For each patient encounter, physicians are instructed to record all diagnoses and indicate drug therapy specifically used to treat each diagnosis. Each patient encounter can generate multiple diagnoses, and there is direct correspondence between the recorded diagnosis and prescribed drug therapy. Physician-reported drug uses include new medications prescribed during that encounter or continued drug therapy that was previously ordered, even if no specific action was taken during that encounter. Drug uses are weighted to reflect national utilization patterns and referred to as drug mentions.

SAMPLED MEDICATIONS AND OBSERVED DIAGNOSES

The NDTI provided data for the top 500 medications in rank order by frequency of NDTI drug mentions in 2001. This analysis considered commonly used medications, including the top 100 by number of NDTI mentions, plus 60 additional randomly selected medications. Medications with over-the-counter availability in 2001 were excluded from this study. This strategy captured prescription medicines from a wide range of therapeutic contexts, but with a preponderance of antibiotics, hypertension therapies, and analgesics because of their prevalence as top sellers. The medications identified in this sample accounted for approximately 56% of all estimated prescription drug use in 2001. Medications were identified by their chemical name, and drug mentions for proprietary and generic versions were combined to give the total mentions for that chemical when at least 1 version was in the original 160-medication sample.

The NDTI lists drug mentions stratified by the top 40 diagnoses associated with each medication. Diagnoses, coded using the *International Classification of Diseases, Ninth Revision, Clinical Modification,*[18] were grouped into 1 of the following 3 categories: FDA approved, off-label with strong scientific support, or off-label with limited or no scientific support. Diagnoses were considered FDA approved if they could be matched to the therapeutic indications reported in the drug's package insert (as compiled in the *Physicians' Desk Reference: 2002*[19]) and assumed to be well supported by scientific evidence. Any diagnosis that could not be matched to a labeled indication was considered off-label.

The degree of supporting evidence was assessed for each off-label indication treated with the medicines in our sample. We used the DRUGDEX system (Thomson Micromedex, Greenwood Village, Colo), a nationally recognized pharmaceutical compendium that describes the efficacy and scientific documentation for labeled and off-label uses of prescription drugs[20] and that has been used to approve payment for off-label uses by Medicaid,[21] to create a database of scientifically supported but off-label indications for each drug in our sample. An indication was considered to be scientifically supported if, according to DRUGDEX, its effectiveness has been shown in controlled trials or observed in clinical settings.[22] All other indications that lacked FDA approval or that did not meet the criteria for having scientific support were considered to be off-label with little or no scientific support.

To give added confidence in our use of DRUGDEX, we independently evaluated the type of evidence used by DRUGDEX in its differentiation of levels of evidence for off-label indications in a subsample of medications. We found that indications our method classified as evidence-based were always supported by clinical trials, whereas those indications with little or no scientific support tended to rely on observational data or case reports. The **Figure** shows the strategy used to classify drug mentions by their level of scientific support.

We were unable to separate patterns of use by the presence of comorbidities that might alter our assessment of whether the drug mention was for an off-label use. Because we were concerned that this might result in misclassification, we examined the comorbidities associated with congestive heart failure to gauge the magnitude of such misclassification. In this example, the concern is that substantial misclassification of angiotensin-converting enzyme inhibitors would result if congestive heart failure were to be reported frequently with other diagnoses for which angiotensin-converting enzyme inhibitors are often prescribed. In 2001, 47% of patients with congestive heart failure were reported to have at least 1 comorbidity, although in only 10% that comorbidity was hypertension or coronary artery disease, the 2 conditions most likely to have an angiotensin-converting enzyme inhibitor reported as therapy. Although we acknowledge this shortcoming, it seems unlikely to dramatically affect our findings.

Drug-specific characteristics including therapeutic class, age, degree of promotion, use as a long- vs short-term therapy, form, and manufacturer were evaluated for their ability to predict off-label use. Medications were assigned to 1 of 13 mutually exclusive functional classes based on the therapeutic intent of its labeled indications. Duration of use was considered long-term (continued use >4 weeks) or short-term (use ≤ 4 weeks). Approval date and patent exclusivity dates for each drug were obtained from the FDA's *Electronic Orange Book, 2003 Vol: Food and Drug Administration*[23] and used to calculate the drug's age and generic availability in year 2001. For medications available in multiple formulations, only that most commonly used in ambulatory settings was considered. Drugs were considered to have a high degree of promotion if they were among the 20 most heavily direct-to-consumer promoted drugs in 2000.[24] Manufacturers represented by fewer than 5 medications among the sampled drugs were grouped, as were manufacturers with similar patterns of off-label use among the sampled medications, and generically available medications were considered to be represented by a single, nonspecific manufacturer. Breadth of therapeutic definition was measured as the total number of approved indications reported in the *Physicians' Desk Reference*.[19]

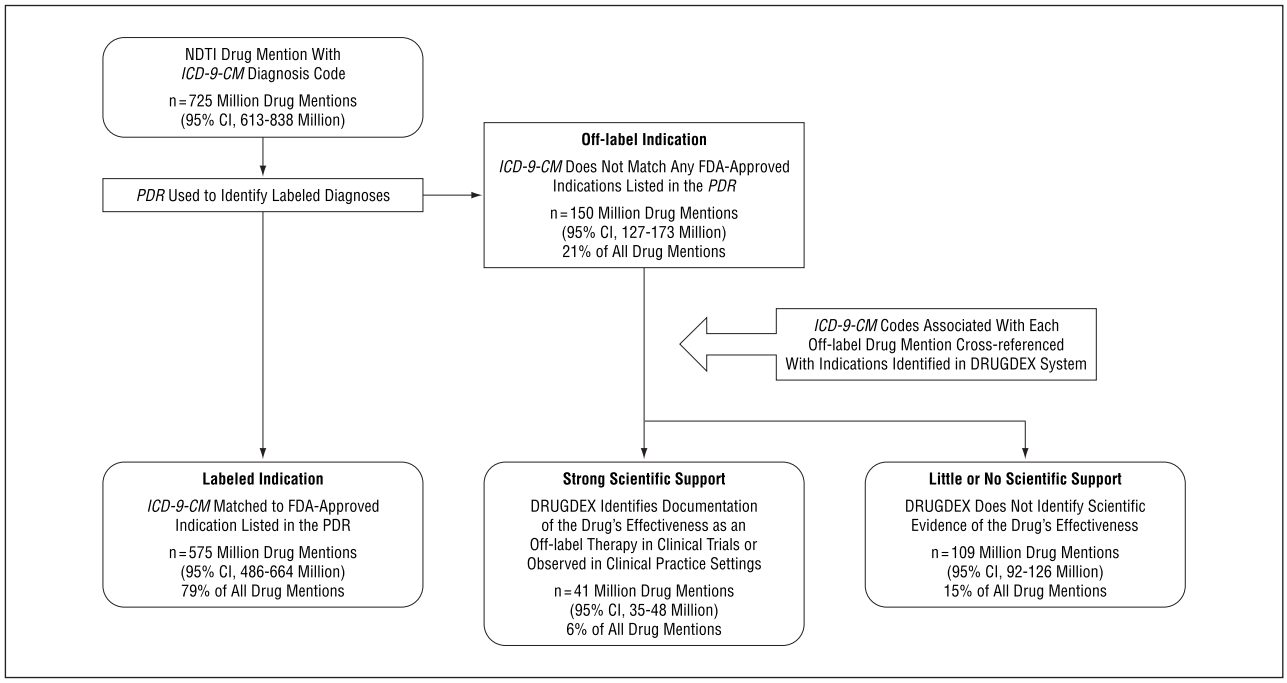

Figure. Assessment of scientific support for each drug-diagnosis combination. Drug mentions are weighted estimates of national prescription drug occurrences based on observed medication use. CI indicates confidence interval; FDA, Food and Drug Administration; *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification*[18]; NDTI, National Disease and Therapeutic Index; and *PDR, Physicians' Desk Reference.*[19]

STATISTICAL ANALYSIS

The unit of analysis was the drug mention; the principle outcome measures were proportion and frequency of off-label prescription among sampled medications. We used multivariate regression to evaluate the ability of specific drug characteristics to predict off-label prescription. This allowed us to test several hypotheses: for example, that increased off-label prescription is associated with particular functional classes, use as a long-term therapy, older drug age, generic availability, a high degree of direct-to-consumer promotion, or manufacturer. The dependent variable was the counted number of drug mentions for off-label uses, and was transformed using a natural logarithm to normalize the distribution. Drugs from the same chemical class share many physical and therapeutic characteristics and, therefore, are not independent with regard to likelihood of prescription. To account for this lack of independence, models were fit clustering on the chemical class with robust variance estimates for the standard error.[25,26] Reported risk ratios (RRs) represent the independent likelihood of that characteristic predicting increased off-label prescription. Data analysis was performed using STATA software, version 8 (StataCorp, College Station, Tex).

RESULTS

The NDTI reported an estimated 725 million total drug mentions among the sampled drugs for year 2001. Although most (575 million [79%]) were for FDA-approved indications, many drug mentions (150 million [21%]) lacked FDA approval for the condition they were used to treat. Therapeutic activity among these medicines was largely supported by scientific evidence, with 85% of all drug mentions (616 million) being FDA-approved or evidence-based off-label uses; 15% of the drug mentions reported herein lacked scientific evidence for the indication they were used to treat. Among off-label mentions, most (73%) lacked evidence of clinical efficacy, and less than one third (27%) were supported by strong scientific evidence (Figure).

Substantial variation in off-label use was observed across functional classes. Considering medication uses with strong and limited or no scientific support together, off-label prescription was rare among medications for glycemic control in diabetes mellitus (<1%) and infrequent among analgesics (6%) and medications to lower lipid levels (7%). Off-label prescription was most common among cardiac medications (antianginals, antiarrhythmics, and anticoagulants) (46%; 95% confidence interval [CI], 39%-53%), anticonvulsants (46%; 95% CI, 39%-53%), and antiasthmatics (42%; 95% CI, 35%-48%) (**Table 1**). Off-label prescription with limited or no scientific support was more common than supported off-label use in all therapeutic classes except diabetes therapies. The greatest disparity between supported and unsupported off-label prescription occurred among psychiatric (4% strong support vs 96% limited or no support) and allergy therapies (11% strong support vs 89% limited or no support).

High volumes of off-label prescription were correlated with high number of total drug mentions for specific drugs ($P<.001$). This is evident in **Table 2**, which shows the top 5 medications by volume of off-label mentions, 3 of which (albuterol sulfate, amoxicillin, and azithromycin) were among the top 5 medications by overall use. Gabapentin had the highest proportion of off-label prescription (83%), followed by amitriptyline hydrochloride (81%) and dexamethasone (79%). Among medications with the highest proportions of off-label use, most lacked evidence of clinical efficacy. This is especially true for gabapentin, where only 20% of its off-label use had strong support compared with 80% with

Table 1. Off-label Prescription and Degree of Scientific Support by Functional Class

Functional Class (No. in Class)	Estimated No. of Mentions in Millions	% of Off-label Mentions* per Class	Off-label Use: Strong Scientific Support — No. of Mentions in Millions	Off-label Use: Strong Scientific Support — % of Off-label Mentions*	Off-label Use: Little or No Scientific Support — No. of Mentions in Millions	Off-label Use: Little or No Scientific Support — % of Off-label Mentions*
Cardiac therapies† (4)	9.5	46	3.8	39	5.8	61
Anticonvulsants (4)	6.6	46	1.1	17	5.4	83
Antiasthmatics (9)	17.7	42	8.3	47	9.4	53
Allergy therapies (9)	14.7	34	1.7	11	13.1	89
Psychiatric therapies‡ (16)	18.0	31	1.0	6	17.0	94
Peptic ulcer and dyspepsia therapies (7)	7.0	30	1.2	17	5.8	83
Antimicrobials (28)	35.5	23	11.6	33	23.9	67
Other§ (15)	13.4	23	3.0	23	10.4	77
Antihypertensives (30)	16.8	14	6.8	41	10.0	59
Women's health therapies|| (8)	2.3	11	0.5	23	1.7	77
Agents to lower lipid levels (6)	2.0	7	0.8	40	1.2	60
Analgesics (15)	6.2	6	1.3	21	4.9	79
Diabetes therapies (8)	0.3	1	0.2	54	0.1	46
Total	**150.0**	**21**	**41.2**	**27**	**108.7**	**73**

*Drug mentions are weighted estimates of national prescription drug occurrences based on observed medication use.
†Includes antianginals (2), antiarrhythmics (1), and anticoagulants (1).
‡Includes antidepressants (9), anxiolytics (5), and antipsychotics (2).
§Includes noninhaled corticosteroids (5), thyroid agents (1), ophthalmologic preparations (2), impotence therapy (1), osteoporosis therapy (1), stimulants (1), antigout therapy (1), antiglaucoma therapy (1), antiemetics (1), and bladder/prostate treatment (1).
||Includes hormone therapy (6) and oral contraception (2).

Table 2. Top 5 Medications by Volume and Proportion of Off-label Prescription*

Top 5 Medications	No. of Off-label Drug Mentions† in Thousands	Off-label Mentions, %† — All	Off-label Mentions, %† — With Strong Scientific Support	Off-label Mentions, %† — With Little or No Scientific Support
No. of off-label mentions				
Albuterol sulfate	*10 087*	53	36	18
Amoxicillin	*8180*	25	13	11
Digoxin	*4423*	66	25	41
Methylprednisolone	*3822*	54	7	47
Azithromycin	*3700*	22	16	5
Proportion of total mentions that were off-label				
Gabapentin	3561	*83*	17	66
Amitriptyline hydrochloride	837	*81*	21	60
Dexamethasone (oral)	2355	*79*	23	56
Isosorbide mononitrate	1532	*75*	48	27
Risperidone	1821	*66*	<1	66
Digoxin	4423	*66*	25	41
Proportion of total mentions with strong scientific support				
Isosorbide mononitrate	1532	75	*48*	27
Albuterol	10 087	53	*36*	18
Famotidine	911	61	*30*	31
Digoxin	4423	66	*25*	41
Ipratropium bromide	1200	47	*25*	22
Proportion of total mentions with limited/no scientific support				
Gabapentin	3561	83	17	*66*
Risperidone	1821	66	<1	*66*
Temazepam	346	63	<1	*63*
Ciprofloxacin hydrochloride (optic solution)	2104	64	2	*62*
Amitriptyline	837	80	21	*60*
Nortriptyline hydrochloride	343	65	5	*60*

*Each section of the table represents the top 5 medications using different metrics to capture varying facets of off-label medication use. Italics represent the numeric metric used to produce the given ranking.
†Drug mentions are weighted estimates of national prescription drug occurrences based on observed medication use.

limited or no support. Conversely, off-label use for several medications was supported by a high degree of scientific evidence. Among the 24 medications for which most (>50%) of the off-label uses were scientifically supported, hypertension therapies were most common (7/21), followed by antimicrobials (4/21) and medications to lower lipid levels (3/21). It is not surprising, then, that 3 hypertension therapies (losartan potassium, atenolol, and a combination of hydrochlorothiazide and metoprolol tartrate) were among those medications with the highest degree of scientifically supported off-label use.

Few drug-specific characteristics were associated with off-label prescription (**Table 3**). Relative to analgesics, diabetes medications (RR, 0.04) were associated with less likelihood of off-label prescription, whereas anticonvulsants (RR, 5.7), psychiatric agents (RR, 4.1), allergy therapies (RR, 4.8), antiasthmatics (RR, 3.4), medications for peptic ulcer and dyspepsia (RR, 4.6), and cardiac medications (RR, 6.8) were associated with increased likelihood of off-label prescription. Other drug characteristics, including age, long-term use, combination therapies, formulation, dosing frequency, direct-to-consumer promotion, and manufacturer, showed few meaningful associations with off-label prescription.

Table 3. Drug-Specific Characteristics Associated With Off-label Prescription

Characteristic	RR (95% CI)	
	Unadjusted	Adjusted*
Analgesics	1.00	1.00
Allergy therapies	4.64 (2.80-7.69)	4.83 (2.19-10.62)
Antiasthmatics	3.33 (1.89-5.88)	3.44 (1.60-7.46)
Anticonvulsants	3.54 (1.98-6.31)	5.67 (2.49-12.91)
Antimicrobials	1.94 (1.02-3.72)	1.96 (1.09-3.54)
Cardiac therapies	6.80 (3.29-14.05)	6.75 (2.66-17.11)
Diabetes therapies	0.02 (0.00-0.11)	0.04 (0.01-0.16)
Peptic ulcer and dyspepsia therapies	3.04 (2.14-4.33)	4.58 (2.17-9.76)
Psychiatric therapies	3.18 (2.04-4.96)	4.08 (1.99-8.36)
Tablet	1.00	1.00
Capsule	1.09 (0.61-1.94)	0.61 (0.41-0.93)
Other medication forms†	0.10 (0.01-0.82)	0.33 (0.14-0.78)
No. of approved indications identified in *PDR*	1.05 (1.02-1.07)	1.03 (1.01-1.05)

Abbreviations: CI, confidence interval; *PDR*, *Physicians' Desk Reference*; RR, relative risk.

*Only drug-specific characteristics with a statistically significant association with off-label prescription are presented here. Adjustments were made for manufacturer, functional class, drug age, degree of direct-to-consumer promotion, use as a long-term therapy, medication form, frequency of use, and generic availability.

†Includes solution/suspension and injectable medication.

COMMENT

Using data from a nationally representative survey of office-based physicians, we found that about 21% of all estimated uses for commonly prescribed medications were off-label, and that 15% of all estimated uses lacked scientific evidence of therapeutic efficacy. We believe that ours is the first study to systematically characterize the extent of off-label prescribing in general outpatient care. The magnitude of off-label use varied widely among specific medications and drug classes, exceeding 50% for some anticonvulsants, psychiatric medications, and antiasthmatics. No more than 30% of the off-label practices we observed were supported by strong scientific evidence.

Many of the observed off-label drug mentions, particularly among medications frequently used off-label, represent a logical extension of the FDA-approved indication. For example, certain unapproved uses of antibiotics could be justified by laboratory studies demonstrating that the disease-causing organism responds to drug therapy. Albuterol, which is approved to treat asthma, is a clinically accepted off-label therapy for physiologically similar chronic obstructive pulmonary disease. Other medications are seen to exhibit a "class effect," such as the use of a particular angiotensin-converting enzyme that lacks approval for congestive heart failure.

In contrast, some of the observed off-label uses were as therapy for indications distinctly different from those for which the drug was approved. Examples include the use of metformin hydrochloride, approved for glycemic control in type 2 diabetes, as a therapy for relatively few patients with polycystic ovary syndrome and gabapentin, labeled for use as an anticonvulsant, as a widely used therapy for chronic nonspecific pain. Substantial heterogeneity remains in the degree to which many off-label practices, even those that seem to represent logical extensions of the labeled indication, are supported by scientific evidence.

Our findings echo those of an earlier study conducted 2 decades ago that considered the degree of evidence supporting a drug's efficacy for a limited number of specific drug-indication pairs.[14] Both studies indicate a need for more extensive postmarketing surveillance to identify non–evidence-based prescribing practices that lacked FDA approval. We suggest that policy makers confront these issues by asking the following questions: (1) What kinds of data could inform our understanding of the clinical and economic implications of off-label and non–evidence-based prescribing? (2) How can such data be collected or accessed once a drug has entered the market? and (3) Should decisions to "sanction" additional therapeutic uses without regulatory scrutiny consider the evidence or be left to market forces?

Differentiating off-label situations that are clinically reasonable from those that may be of concern is an essential first step. Such issues are at the forefront of prescription drug policy in Europe, where various systems have been established to monitor medication use after initial approval by regulatory authorities.[27] Regulators in Britain may label new drugs with a black triangle, signaling physicians to exercise caution when prescribing them; they can also monitor outcomes through a voluntary database of physicians' prescribing experiences. In France, pharmacovigilance centers track postapproval prescribing of drugs, whereas the European Medicines Agency can require drug manufacturers to collect and analyze postapproval surveillance data and mandate license renewal at shorter time intervals. These examples are designed primarily to protect patient safety, although simi-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.