Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Data Sources

Data	Source
Therapeutics approved between 2001 and 2010 and class (i.e., pharmaceutical and biologic)	Drugs@FDA: Classified by applying an algorithm to the Drugs@FDA database downloaded from FDA website that identifies novel pharmaceuticals (i.e., subgroup of new drug applications labelled as new molecular entities) and all novel biologics (i.e., all biologic license applications) approved between January 1, 2001 and December 31, 2010.
Therapeutic area	FDA approval letters + manual classification: Assigned based on clinical experience after abstracting the indication for which each novel therapeutic was first approved for use from approval letters available on the FDA website.
Orphan drug status	Orphan Drug Product Designation Database: Searched manually to identify drugs with orphan status for the initially approved indication.
Priority review status	Drugs@FDA: Identified using an indicator variable provided in the database.
Accelerated approval	FDA approval letters: Identified by systematically reviewing FDA approval letters, which indicate those therapeutics receiving accelerated approval.
Total review time	FDA approval letters: Abstracted submission dates and decision dates for all review cycles for all therapeutics, allowing total review time to be calculated.
Prescription Drug User Fee Act deadline	Calculated according to priority review status (see eTable 2).

eTable 2. Iterations of the Prescription Drug User Fee Act (PDUFA) and Associated Goal Review Times That Were Used to Identify Near–Regulatory Deadline Approvals

			Goal review time, months	
	Start date	End date	Standard review	Priority review
PDUFA I/II	Prior to January 1, 2001	September 30, 2002	12	6
PDUFA III	October 1, 2002	September 30, 2007	10	6
PDUFA IV	October 1, 2007	September 30, 2012	10	6

Note: PDUFA refers to the Prescription Drug User Fee Act, which was initially enacted into law in 1992 and has been re-authorized every five years until the present day. The numerals that follow this abbreviation indicate the iteration of PDUFA that is described in each row of the table.

eTable 3. Exclusion of Nonunique Safety Events

Our search strategy identified safety communications affecting 50 novel therapeutics. Of these, safety communications for 8 drugs were excluded because the communication did not constitute a unique postmarket safety event (see table below). The most common rationale for exclusion was a contemporaneous more serious postmarket safety event (i.e., boxed warning or withdrawal). After excluding these safety communications, there were 42 novel therapeutics that were subject to a drug safety communication that addressed unique postmarket safety signals.

Therapeutic	Safety signal noted in drug safety communication	Rationale for exclusion
Abobotulinumtoxin	Distant spread of toxin	Associated with contemporaneous boxed warning
Alemtuzumab	Immune thrombocytopenic purpura	Safety signal only applies to use of drug in off-label indication
Efalizumab	Progressive multifocal leukoencephalopathy	Associated with contemporaneous withdrawal
Galantamine	Increased mortality	Unsubstantiated postmarket safety signal
Natalizumab	Progressive multifocal leukoencephalopathy	Associated with contemporaneous boxed warning
Ofatumumab	Hepatitis	Associated with contemporaneous boxed warning
Pimecrolimus	Increased risk of cancer	Associated with contemporaneous boxed warning
Valdecoxib	Increase rate of cardiovascular events and gastrointestinal bleeding	Associated with contemporaneous withdrawal

eTable 4. Therapeutics With Multiple Unique Postmarket Safety Events

There were 19 novel therapeutics that experienced multiple postmarket safety events. For 5 novel therapeutics (highlighted in green), there was an escalation of the initial safety event to a more serious level (i.e., a safety communication followed by a boxed warning or a boxed warning followed by a withdrawal on the basis of the safety signal first identified in the safety communication). The remaining 14 novel therapeutics experienced multiple postmarket safety events for unique safety risks: 4 were first subject to a safety communication that was followed by a boxed warning for a different safety risk (highlighted in blue), 1 was first subject to a boxed warning and would later be withdrawn for a different safety risk (highlighted in red), while the remaining 9 were first subject to a boxed warning and later a safety communication for a different safety risk.

Therapeutic	First safety signal	Second safety signal
Adalimumab	Boxed warning (Nov ’09): Malignancy	Safety communication + Boxed warning (Sept ‘11): Risk of Listeria and Legionella infection
Aripiprazole	Boxed warning (Feb ’06): Increased mortality in elderly patients with dementia-related psychosis; Suicidality and anti-depressant drugs	Safety communication (Feb ’11): Risk for extrapyramidal signs and withdrawal in newborns when used in pregnancy
Certolizumab	Boxed warning (Nov ’09): Malignancy	Safety communication + Boxed warning (Sept ‘11): Risk of Listeria and Legionella infection
Dabigatran	Safety communication (Dec ’12): Contraindication for use in patients with mechanical heart valves	Boxed warning (Apr ’13): Premature discontinuation leads to thrombotic events
Darbepoetin	Boxed warning (Mar ’07): Increased risk of death	Safety communication (Jun ’11): Dosing in chronic kidney disease (due to increased risk of cardiovascular events in this patient population)
Dronedarone	Safety communication (Jan ’11): Hepatotoxicity	Boxed warning (Dec ’11): Serious cardiovascular events
Duloxetine	Boxed warning (Feb ’05): Suicidal thoughts and behaviors in children and adolescents	Safety communication (Jul ’06): Risk of serotonin syndrome when used with triptan
Efalizumab	Boxed warning (Oct ‘08): Risk of progressive multifocal leukoencephalopathy; Risk of serious infection	Withdrawal (Apr ’09): Risk of progressive multifocal leukoencephalopathy
Ethinyl Estradiol; Norelgestromin	Safety communication (Jan ’08): Risk of venous thromboembolism	Boxed warning (Mar ’11): Risk of venous thromboembolism; Uncertainty about the effect of the pharmacokinetic profile of ethinyl estradiol delivered by the transdermal route
Formoterol	Safety communication (Nov ’05): Increased risk of bronchospasm	Boxed warning (Jun ’06): Asthma-related death
Gemifloxacin	Boxed warning (Oct ’08): Tendonitis and tendon rupture	Safety communication (Aug ’13): Peripheral neuropathy
Golimumab	Boxed warning (Nov ’09): Malignancy	Safety communication + Boxed warning (Sept ‘11): Risk of Listeria and Legionella infection
Lenalidomide	Safety communication (May ’12): Increased risk of cancer	Boxed warning (Sept ’14): Arterial thromboembolism

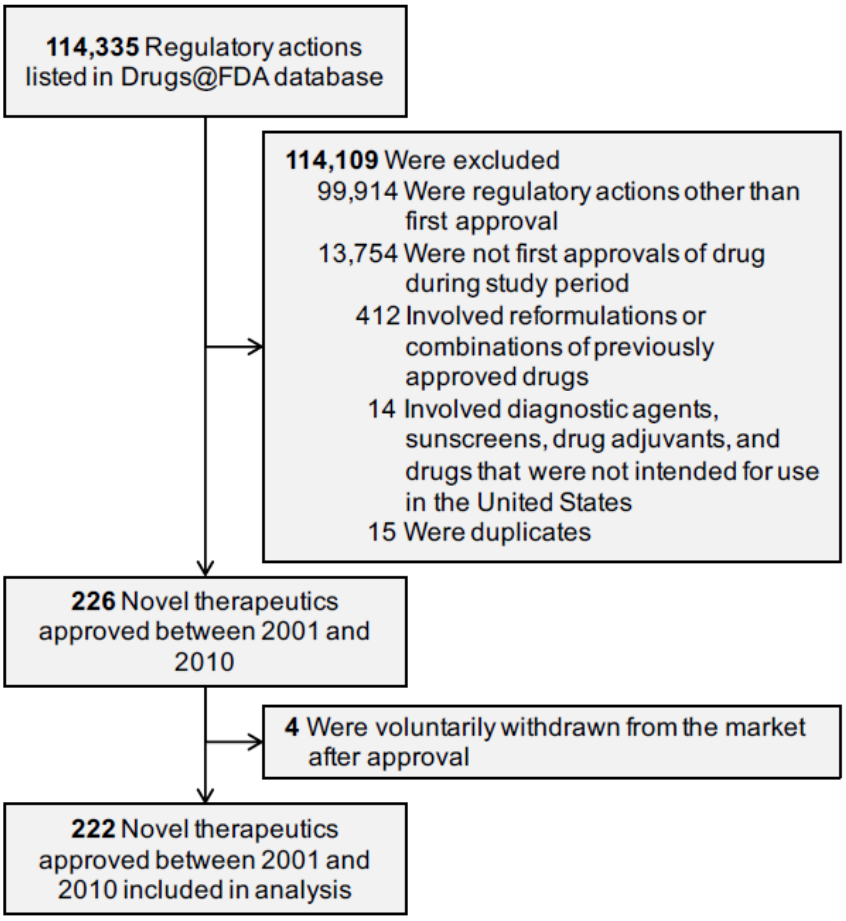
Omalizumab	Boxed warning (Jul ’07): Anaphylaxis	Safety communication (Sept ’14): Increased risk of CV events
Telithromycin	Safety communication (Jun ’06): Liver toxicity	Boxed warning (Feb ’07): Contraindicated in patients with myasthenia gravis
Tigecycline	Safety communication (Sept ’10): Increased risk of death	Boxed warning (Sept ’13): Mortality
Varenicline	Safety communication (Feb ’08): Neuropsychiatric symptoms	Boxed warning (Jul ’09): Serious neuropsychiatric events
Valdecoxib	Boxed warning (Nov ‘04): Serious skin reactions	Withdrawal (Apr ’05): Cardiovascular events
Ziprasidone	Boxed warning (Aug ’05): Increased mortality in elderly patients with dementia-related psychosis	Safety communication (Feb ’11): Risk for extrapyramidal signs and withdrawal in newborns when used in pregnancy

eTable 5. Postmarket Safety Events at 10 Years and Associations Between Events and Characteristics of Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010, Limited to Therapeutics With a First-in-Class Approval in 2001 or Later[a]

Characteristic	Proportion Affected by a Postmarket Safety Event at 10 y, % (95% CI)	Bivariate analysis		Multivariable analysis	
		Difference in Proportion Affected by a Postmarket Safety Event at 10 y, % (95% CI)	*P* Value	Incidence Rate Ratio (95% CI)	*P* Value
Drug class					
Pharmaceutical	25.7 (17.2-37.3)	0 [Reference]		1 [Reference]	
Biologic	32.1 (18.2-52.7)	6.4 (-13.5-26.5)	.53	4.8 (1.4-16.3)	.01
Therapeutic area					
Cancer and hematology	15.6 (6.8-33.5)	0 [Reference]		1 [Reference]	
Autoimmune, musculoskeletal, and dermatology	22.2 (6.1-63.5)	6.6 (-23.3-36.5)	.67	0.81 (0.18-3.7)	.79
Cardiovascular, diabetes, and hyperlipidemia	31.6 (13.2-64.1)	16.0 (-12.7-44.7)	.27	2.2 (0.55-8.6)	.27
Genitourinary and renal	n/a	n/a	n/a	n/a	n/a
Infectious disease	25.9 (9.1-60.9)	10.3 (-18.0-38.6)	.48	2.0 (0.54-7.5)	.30
Neurology	60.0 (24.7-94.8)	44.4 (-0.37-89.1)	.05	4.2 (1.1-16.2)	.04
Psychiatry	80.0 (41.8-99.2)	64.4 (27.1-101.6)	<.001	9.5 (2.7-33.1)	<.001
Other	26.9 (13.9-48.3)	11.3 (-9.9-32.5)	.30	1.4 (0.44-4.2)	.60
Priority vs standard review					
Standard review	32.3 (21.9-45.9)	0 [Reference]		1 [Reference]	
Priority review	21.0 (11.5-36.5)	11.3 (-5.9-28.4)	.20	1.4 (0.54-3.4)	.51
Accelerated vs not accelerated approval					
Not accelerated	27.2 (18.9-38.1)	0 [Reference]		1 [Reference]	
Accelerated	29.4 (13.4-56.9)	2.2 (-21.4-25.9)	.18	2.3 (0.81-6.4)	.12
Orphan vs not orphan status					
Not orphan	33.4 (22.9-46.9)	0 [Reference]		1 [Reference]	
Orphan	19.1 (10.0-34.5)	14.3 (2.6-31.2)	.10	0.41 (0.16-1.1)	.07
Near–regulatory deadline vs regular approval					
Regular	25.4 (17.2-36.5)	0 [Reference]		1 [Reference]	
Near–regulatory deadline	37.5 (20.7-61.5)	12.1 (-10.8-35.0)	.30	2.0 (0.92-4.2)	.08
Regulatory review time, d					
<200	18.2 (8.6-36.1)	18.6 (-1.4-38.5)	.07	0.37 (0.14-1.0)	.05
200-399	36.8 (23.9-53.6)	0 [Reference]		1 [Reference]	
≥400	26.9 (13.9-48.3)	9.8 (-12.9-32.5)	.40	1.2 (0.50-2.7)	.72

[a] Data based on 42 postmarket safety events among 103 novel therapeutics.

eFigure. Flow Diagram Showing Approach to Identifying Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010



eBox 1. Protocol for Identification of Incremental Boxed Warnings

- To determine if an incremental boxed warnings occurred during the study period:
  - Identify relevant NDA/BLA in Drugs@FDA database
  - Review most recent drug label. If a boxed warning is present, record:
    - Date of the label was last updated
    - Indications for which the boxed warning was issued (listed in capitals in title of boxed warning)
  - When boxed warning is identified in most recent label, use the Drugs@FDA database to identify first available drug label (i.e., from time of approval) and determine if a boxed warning is present. If a boxed warning is noted, record:
    - Date of the label was last updated
    - Indications for which the boxed warning was issued (listed in capitals in title of boxed warning)
  - Determine if incremental boxed warning was added to drug label in post-market period:
    - If boxed warning present on most recent label, but not at time of approval:
      - Note incremental boxed warning detected
      - Identify when labeling change that introduced the boxed warning occurred by reviewing drug labels in chronological order (i.e., date associated with the first label posted on Drugs@FDA that contains a boxed warning)
    - If boxed warnings present in both most recent label and at time of approval:
      - Compare indications for which boxed warnings were issued and determine if a new indication has been added to the boxed warning. If so, note incremental boxed warning detected.
      - Identify when labeling changes that introduced the incremental boxed warning occurred by reviewing drug labels in chronological order (i.e., date associated with the first label posted on Drugs@FDA that contains a boxed warning)

eBox 2. Protocol for Identification of Safety Communications

- To determine if a safety communication occurred during the study period:
  - Identify when FDA has alerted the *prescribing community* about a change in the balance of risks and benefits for an approved drug (using the FDA's online database)
    - Any Drug Safety Communication (this encompasses all notifications after 2010)
    - Healthcare Professional Sheets / Information for Healthcare Professionals / Public Health Advisories (prior to 2010).
    - Early communications were not included because the safety signals discussed in such communications are preliminary and have not been substantiated.
    - Exclude any alert containing information that has not been substantiated (e.g., safety communications updating prescribers that the agency's review of the risk of cancer associated with a certain drug's use is ongoing, and that no action has been taken; n.b., do not exclude any notification that describes safety action taken by FDA, such as labeling change, even if review of data is ongoing).
    - Exclude any alert that was not triggered by new safety information (e.g., new clinical trial questioning the efficacy of a drug)