Characteristics of Evidence Supporting Approval of Supplemental Indications for Prescription Drugs in the United States, 2005-2014

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Data Statement: All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency: ASK affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethics Approval and Patient Consent: Ethics approval was not required for this study because it was based on publicly available data and involved no individual patient data collection or analysis.

Abstract

Objective: Because prescription drugs are frequently approved and prescribed for supplemental indications following their initial approval, we sought to characterize the types of comparators and endpoints used in efficacy trials for approvals of supplemental indications, as compared to the data supporting these agents' originally approved indications.

Design/Setting: Analysis of supplemental indications approved from 2005-2014 for novel therapeutics, using publicly accessible data from the Food and Drug Administration (FDA).

Main outcome measures: We assessed types of comparators (active, placebo, historical, none) and endpoints (clinical outcomes, clinical scales, surrogate) in the efficacy trials for these drugs' supplemental and original approvals.

Results: Our cohort included 295 supplemental indications. Thirty percent (41/136) of approvals for new indications were supported by efficacy trials with active comparators, compared with 51% (47/93) of modified use approvals and 11% (7/65) of approvals expanding the patient population ($p<0.0001$), almost all of which related to pediatric patients (61/65, 94%). Trials using clinical outcome endpoints led to approval for 32% (44/137) of supplemental approvals for new indications, 30% (28/93) of modified indication approvals, and 22% of expanded population approvals ($p=0.29$). Orphan drugs had supplemental approvals for 40 non-orphan indications, which were supported by similar proportions of trials using active comparators and clinical outcome endpoints (28% [11/40] vs 24% [10/42], $p=0.70$; 25% [10/40] vs 31% [13/42], $p=0.55$; respectively).

Conclusions: Wide variations were seen in the evidence supporting approval of supplemental indications, with the fewest active comparators and clinical outcome endpoints used in trials leading to supplemental approvals that expanded the patient population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

New prescription drugs are approved by regulatory agencies like the U.S. Food and Drug Administration (FDA) on the basis of pivotal clinical trials that vary in some of their essential features, including type of comparator and study endpoint. Approvals based on single-arm trials or that use surrogate endpoints are risky to patient since their efficacy and safety may not be fully characterized.

After a prescription drug has been authorized, it may subsequently be approved and prescribed for supplemental indications. The legal evidentiary standard for supplemental approvals is the same as for original approvals.

WHAT THIS STUDY ADDS

Prescription drugs approved for supplemental indications by the FDA were supported by low rates of clinical trials using active comparators or study endpoints directly related to patient function or mortality, especially among supplements that expanded the drugs' approved patient populations.

Robust post-approval surveillance of a drug's safety and efficacy for its supplemental indications, in addition to re-examination of current legislative incentives to better encourage higher-quality pre-approval trials, may help reduce the risk to patients from using prescription drugs for their approved supplemental indications.

Before a new prescription drug can be made widely available to patients in the US, the Food and Drug Administration (FDA) must review a vast array of data relating to its use submitted as part of a New Drug Application or Biologic Licensing Application, including clinical trials testing the drug in the population for which it is intended to be marketed. By law, such trials must show both the drug's safety and substantial evidence of its efficacy. Recent studies of the pivotal clinical trials used to meet this standard indicate that approximately half of new drugs are approved after being tested against placebos and a similar number in single-arm, uncontrolled trials.[1] Other reviews have found that half of all new drugs are approved based on trials using surrogate outcomes, including biomarkers like LDL cholesterol or hemoglobin A1c, rather than actual clinical outcomes, such as mortality or clinical cure.[2] The clinical trial evidence supporting new drug approval also varies by disease type, with cancer agents and drugs for rare diseases more commonly tested in less robust non-randomized or unblinded studies or studies using surrogate endpoints compared to other therapeutic areas.[3 4]

After their initial approval, many new drugs are approved for additional clinical indications. Such approvals can occur if the manufacturer submits new data via a so-called supplemental New Drug Application (sNDA) or supplemental Biologic Licensing Application (sBLA). For example, imatinib (Gleevec) was initially approved in 2001 for the treatment of chronic myeloid leukemia and was subsequently approved for nine additional indications, including gastrointestinal stromal tumor and pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia.[5 6] In 2014, the FDA approved 40 new supplemental indications for already-marketed drugs, compared with original approvals of 44 novel small molecule and biologic agents during the same period.[7 8] In some cases, the rate of prescribing for drugs' supplemental indications can exceed their original indications.[9]

The legal standard underlying FDA approval remains consistent for original and supplemental indications. Previous research on supplemental approvals has found that the average regulatory review times are shorter than for their original indications.[10 11 12] However, the rigor of trials that support drugs' supplemental indications has not been analyzed. We sought to determine whether the evidence supporting drugs' supplemental indications differ substantially from the characteristics of studies underlying the indications for which the drugs were originally approved. We characterized the quality of clinical trial evidence supporting the supplemental indications of novel agents, focusing on study comparators and trial endpoints. Finally, we compared the evidence supporting the new uses with the studies providing the basis of approval for these agents' original indications.

Methods

Study Sample

The FDA lists all sNDAs and sBLAs on its Drugs@FDA database.7 One author (BW) manually extracted all supplemental approvals occurring between 2005 and 2014 from this database, excluding supplements categorized by the FDA as relating to "Labeling Revisions" and "Manufacturing Change or Addition," which focus mainly on administrative and/or logistical modifications. The FDA letters accompanying these approvals were then examined to exclude supplemental approvals unrelated to a new or modified indication, such as inclusion in the drug label of additional clinical data supporting an already-approved indication (**Figure 1**).

We excluded duplicates, counting only once an approval of the same supplemental indication relating to multiple formulations of the same active ingredient. We also excluded all prescription drugs and biologics that were not originally approved as novel therapeutic agents

(new molecular entities and original therapeutic biologics; n=132) as well as all contrast and diagnostic products (n=11). We were left with 295 supplemental approvals relating to 164 unique drugs.

Characteristics of Supplemental Indications

For each supplemental approval, we determined its primary therapeutic area by consensus. We also classified each supplemental approval into one of three mutually-exclusive categories: (1) new indication, meaning that no similar use was ever previously approved for the agent; (2) modification of an already-approved indication (*e.g.*, a drug initially approved for adjunctive therapy in treatment of partial-onset seizures was now also indicated for use as monotherapy in this condition); or (3) expansion in patient population (*e.g.*, a drug previously indicated for treatment of adult Crohn's disease was now also approved for use in all patients 6 years and older).

We then used the Drugs@FDA database to gather information on each supplemental approval's date and chemical type (small-molecule or biologic). Both the Drugs@FDA database and FDA Orphan Drug Product database[13] were employed to determine whether the FDA granted orphan drug designation for each supplemental application as well as for each study drug at the time of original approval. Orphan drug designation has been granted by the FDA Office of Orphan Product Development to drugs that treat diseases affecting fewer than 200,000 individuals in the US each year.[14] This designation is indication-specific, so granting such a designation for a drug's original approval should not carry over to all its supplemental indications. For example, onabotulinumtoxinA (Botox), which received orphan drug designation

for its initially-approved indications, was approved in 2013 for treatment of overactive bladder, a far more prevalent condition.[15 16]

Characteristics of Efficacy Studies

We first sought to assess the characteristics of the clinical evidence underlying supplemental approvals in the same way that other investigators have studied such data in original drug approvals: using publicly available FDA medical reviews, which are documents that explore in detail the efficacy and safety demonstrated in clinical trials by the novel agent. However, we found medical reviews for only 20% of all supplemental approvals during our study time period, with such information available for 1 of 26 and 0 of 40 supplemental approvals from 2013 and 2014, respectively. Instead, we assessed the supporting clinical evidence for all supplemental approvals at the time of approval by accessing the earliest FDA drug label in the Drugs@FDA database that mentioned the newly-approved use.

We determined the study comparator used in the major studies that were conducted to establish the drug's evidence of efficacy, as designated in the drug labels. We first classified the comparators as active, placebo, historical, or none. Drugs included active comparator data if at least 1 major efficacy trial compared the drug (drug A) versus an alternative therapeutic option (*e.g.*, drug A vs drug B; drug A vs standard of care).[2] Drug supplements were classified as being supported by placebo comparator trials if no major efficacy studies relating to the supplemental approval included active comparators and at least one study included a placebo comparator (*i.e.*, drug A vs placebo). Historical controlled trials compared patients treated with the drug of interest with those in earlier cohorts, either treated or untreated. Drugs tested in single-arm trials

or drugs with multiple doses evaluated without separate comparators were classified as having no comparators.

We then determined the main endpoints in these efficacy trials and classified the endpoints as clinical outcomes, clinical scales, or surrogate outcomes.[2] Clinical outcomes measure mortality or patient function and include markers such as death or incidence of disease. Clinical scales serve as quantitative gradations for patient symptoms, such as the American College of Rheumatology criteria to measure response to rheumatoid arthritis.[17] Surrogate endpoints are intermediate outcomes intended to predict clinical benefit or harm, and include laboratory values and other measures such as tumor size. In cases where multiple types of endpoints were used in the efficacy trials, we classified the endpoint under the more robust outcome.

Finally, for each supplemental approval, we evaluated the characteristics of the major efficacy trials supporting the drugs' originally approved indications using the same classification frameworks. We used the Drugs@FDA database and Physicians' Desk Reference to gather the initial or earliest accessible drug labels for each therapeutic.

We were unable to assess additional characteristics of efficacy trials, including blinding, trial size, and study duration, because such information was not included or inconsistently described in a substantial number of the drug labels we evaluated.

Statistical Analysis

We performed pre-specified chi-square tests of the study comparators and endpoints based on the supplement category, chemical type, therapeutic area, and orphan drug status. We also performed chi-square tests to compare efficacy trials for supplemental approvals with

similar data from the original indications. Each drug's originally approved indication was counted only once for each comparison, even if the drug featured multiple supplemental approvals.

Results

The FDA approved 295 supplemental indications between 2005 and 2014, representing 164 unique drugs (**Appendix Table 1**). Fifty-eight (35%) drugs had two or more approved new uses during our study period. The annual number of supplemental approvals ranged from 20 in 2012 to 48 in 2006 (**Figure 2**). New indications constituted 137 (46%) of the supplemental approvals. The remainder were modifications to previously-approved indications, including 93 (32%) modifications to the originally approved use and 65 (22%) supplemental approvals that specifically expanded the patient population of the originally approved use, nearly all of which (61, 94%) related to pediatric patients. Most of the supplemental approvals were for small-molecule drugs (210, 71%) while 85 (29%) were for biologics (**Table 1**). The top therapeutic areas were oncology (80, 27%); infectious disease (44, 15%); and cardiovascular disease and its risk factors, including diabetes, dyslipidemia, and hypertension (35, 12%). Sixty (20%) of the supplemental approvals were granted orphan drug designation.

Clinical Evidence Supporting Supplemental Approvals

Supplemental approvals of small-molecule and biologic drugs were supported by a similar proportion of active comparator trials (33% [68/209] vs 32% [27/85], p=0.90), while trials relating to small-molecule drugs used clinical outcomes more often than trials relating to biologics (33% [70/210] vs 19% [16/85], p=0.01) (**Tables 2 and 3**).

There were significant differences in study comparators among the different therapeutic areas. The number of active comparator studies ranged from zero out of 34 supplemental approvals for psychiatric drugs to 55% (44/80) among drugs targeting cancer (p<0.0001). Clinical outcomes were most often used in trials supporting supplemental approvals of drugs relating to neurological conditions (11/23, 48%) and infectious diseases (20/44, 45%). Drugs used in oncology contained the highest proportion of supplemental approvals supported exclusively by trials using surrogate outcomes (70%, 56/80).

Supplemental approvals with orphan drug designations and those not designated as orphan drugs were both supported by active-controlled trials about one-third of the time (28% [17/60] vs 33% [78/234], p=0.46). In addition, about one-third of orphan-designated supplemental approvals (35%, 21/60) were supported exclusively by uncontrolled or historically controlled trials. Orphan drug supplemental approvals were also supported by a lower proportion of trials using clinical outcome endpoints than non-orphan approvals (18% [11/60] vs 32% [75/235], p=0.04) and a higher proportion of studies using surrogate outcomes (57% [34/60] vs 35% [82/235], p=0.002).

New use supplemental approvals (N=137)

Among the subgroup of supplemental approvals relating to new indications, at least one trial containing an active comparator was found in 30% (41/136) of approvals, while 57% (77/136) were supported by placebo-controlled studies (a study comparator was not identifiable in one case). Uncontrolled trials led to the approval of 13% (18/136) of indications.

Clinical outcome endpoints were used in at least one trial for 32% (44/137) of supplemental approvals for new indications, while 31% (43/137) were supported by trials using

clinical scale endpoints. Trials using surrogate outcomes formed the basis of approval for 36% (50/137).

Modified use (N=93)

Among the subgroup of supplemental approvals relating to modified indications, approximately half (47/93, 51%) were supported by an active comparator study, while 42% (39/93) were approved based on placebo-controlled trials, and 6% (6/93) were supported by uncontrolled or historically-controlled trials.

Thirty percent (28/93) of the supplemental indications were supported by trials using clinical outcome endpoints. One-quarter (25%, 23/93) were supported by studies using clinical scale endpoints while 44% (41/93) were approved based on trials using surrogate outcomes.

Expanded patient population (N=65)

Among the subgroup of supplemental approvals relating to expanded patient populations (nearly all in children), active comparator trials were used to support 11% (7/65). Forty percent (26/65) were approved based on placebo-controlled trials, while uncontrolled trials formed the basis of approval of an additional 28% (18/65). Ten supplemental approvals (15%) had no efficacy trials.

Trials containing clinical outcome endpoints were found in 22% (14/65) of approvals, while 26% (17/65) of supplemental approvals were supported by studies containing clinical scale endpoints. Efficacy trials using surrogate outcome endpoints formed the basis of approval for 38% (25/65) of the supplemental indications.

Comparing Supplemental and Original Approvals

The 164 drugs in the cohort were originally approved for 202 indications. Fewer supplemental approvals for new use indications were supported by trials using active comparators than the drugs' originally approved indications (30% [41/136] vs 47% [53/113], p=0.007) and more were supported by placebo-controlled studies (57% [77/136] vs 41% [46/113], p=0.01). Fewer supplemental approvals that expanded the approved patient population were supported by active comparator trials (11% [7/65] vs 47% [27/58], p<0.0001) and trials using clinical outcome endpoints (22% [14/65] vs 47% [28/59], p=0.002) compared to the evidence supporting these agents' originally approved indications.

Supplemental approvals for drugs treating both infectious diseases and psychiatric conditions were supported by a lower proportion of trials using active comparators than original approvals in these therapeutic areas (48% [21/44] vs 76% [31/41], p=0.008; 0% [0/34] vs 62% [8/13], p<0.0001), while the rate of active comparator studies was higher for oncology supplemental approvals compared to original approvals for drugs in this disease category (55% [44/80] vs 32% [13/41], p=0.02).

A similar proportion of supplemental approvals and original approvals granted orphan drug status were supported by trials using active comparators (28% [17/60] vs 24% [10/42], p=0.61) and clinical outcome endpoints (18% [11/60] vs 31% [13/42], p=0.14). Drugs granted orphan drug designation at the time of original approval were subsequently approved for 77 supplemental indications, 40 (52%) of which were indications not related to rare diseases. Compared to the original orphan approvals, these non-orphan supplemental approvals were supported by a similar proportion of active comparator trials (28% [11/40] vs 24% [10/42], p=0.70) and studies using clinical outcome endpoints (25% [10/40] vs 31% [13/42], p=0.55).

Discussion

Our analysis of clinical trials demonstrating the efficacy of FDA-approved supplemental indications between 2005 and 2014 found low rates of active comparator and clinical outcome endpoint use, similar to other studies evaluating such features for original approvals. Supplements that expanded a drug's approved patient population were supported by the fewest active comparator trials and studies using clinical outcome endpoints. Drugs granted orphan drug designations at the time of original approval had the same rates of active comparator and clinical endpoint use in subsequently approved indications, even when such supplemental approvals were for non-rare conditions.

Almost all of the supplements expanding a drug's approved patient population were for pediatric patients, and nearly half of these supplemental approvals were supported by uncontrolled studies or no additional clinical studies, with approval based on extrapolation from adult studies alone. Uncontrolled studies or studies testing surrogate endpoints are likely to be completed relatively quickly and inexpensively. Yet most of these studies will lead to 6 months of additional market exclusivity under the Best Pharmaceuticals for Children Act, which can be extremely lucrative for the sponsor.[18 19] While we do not conclude that any of these approvals were mistaken, pediatric patients have unique physiologies and pharmacokinetic properties that may require more rigorous trials to confirm the efficacy and safety of drugs previously approved only for use in adults.[20 21 22] Policymakers should re-examine the 6-month exclusivity incentive, and perhaps replace it with an incentive that better encourages higher-quality trials.

Our study findings indicate the importance of post-approval surveillance of drugs' supplemental indications, particularly those that expand the eligible patient population. The

FDA's Sentinel Initiative is a nationwide active surveillance program which draws upon multiple healthcare data sources and has the potential to shorten the time needed to identify safety issues related to drug and medical products.[23 24] In addition to these large-database safety studies, timely confirmatory prospective post-approval efficacy trials of the supplemental indications are needed. However, FDA-required post-approval confirmatory studies are frequently delayed or not completed because the FDA has limited power to enforce these commitments.[25 26]

Among drugs originally approved using orphan drug designations, we expected the trials leading to their non-orphan supplemental approvals to be more robust. Trials leading to the original approval of drugs with orphan drug or other special developmental designations infrequently use clinical endpoints or active comparators.[27] Such study designs are ethically and practically justified when no alternative therapies are available in order to facilitate earlier patient access to potential therapeutic advances, despite the increased likelihood of postmarketing safety problems associated with expedited drug approvals[28] However, we found that many drugs approved via the orphan drug designation were tested in trials not using clinical endpoints or active comparators for supplemental indications, even when those supplemental indications do not qualify for the same designation. For example, eltrombopag, originally approved using orphan drug designation in 2008 for the treatment of thrombocytopenia in patients with immune thrombocytopenic purpura, was later approved for thrombocytopenia in patients with hepatitis C, a non-rare condition. The two efficacy trials in eltrombopag's supplemental approval used placebo comparators and surrogate outcome endpoints.[29] The clinical imperative to expedite approval by permitting such strategies as surrogate endpoints is reduced in the case of supplemental indications since the drugs are available for off-label use.

Communication to providers and patients of the nature of the evidence supporting supplemental approvals can help promote knowledge of drugs' expected benefits and risks. One step toward such enhanced communication would be greater transparency of the medical reviews relating to supplemental approvals, which faithfully summarize the clinical evidence in the application. We found that 80% of FDA medical reviews for supplemental approvals were not accessible. Other researchers have suggested the inclusion of a summative statement or grade to indicate the quality of evidence supporting a drug's initial approval.[2] Such statements are also needed for supplemental approvals.

Our study has several limitations. First, we only included supplemental approvals for drugs originally approved as novel therapeutic agents, so our study findings may not be representative of the evidence base supporting all supplemental approvals. Second, we assessed the clinical trial evidence supporting supplemental and original approvals using FDA-approved drug labels rather than the detailed FDA medical reviews. However, the distribution of study comparators and clinical endpoints for the originally approved indications in our study, including proportion of supporting trials using active comparators and clinical outcome endpoints, is consistent with prior research.1 2 In addition, since we assessed the data contained within drug labels for supplemental and original approvals, the results should reflect the degree to which the clinical evidence differs between these two sets of indications. Finally, we only assessed evidence supporting the efficacy of supplemental and original approvals, focusing on the trials' comparators and endpoints. Other important aspects of preapproval trials, including randomization, blinding, and duration, should be explored in future studies.

Nearly 300 supplemental applications relating to approved prescription drugs have been approved in the last decade, providing FDA validation for a wide range of uses beyond the

drugs' original indications. However, the high degree of heterogeneity of supporting evidence for supplemental approvals underscores the need for a robust system of post-approval drug monitoring as well as reexamination of existing legislative incentives to promote the optimal delivery of evidence-based medicine.

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Figure 1. Construction of Study Sample

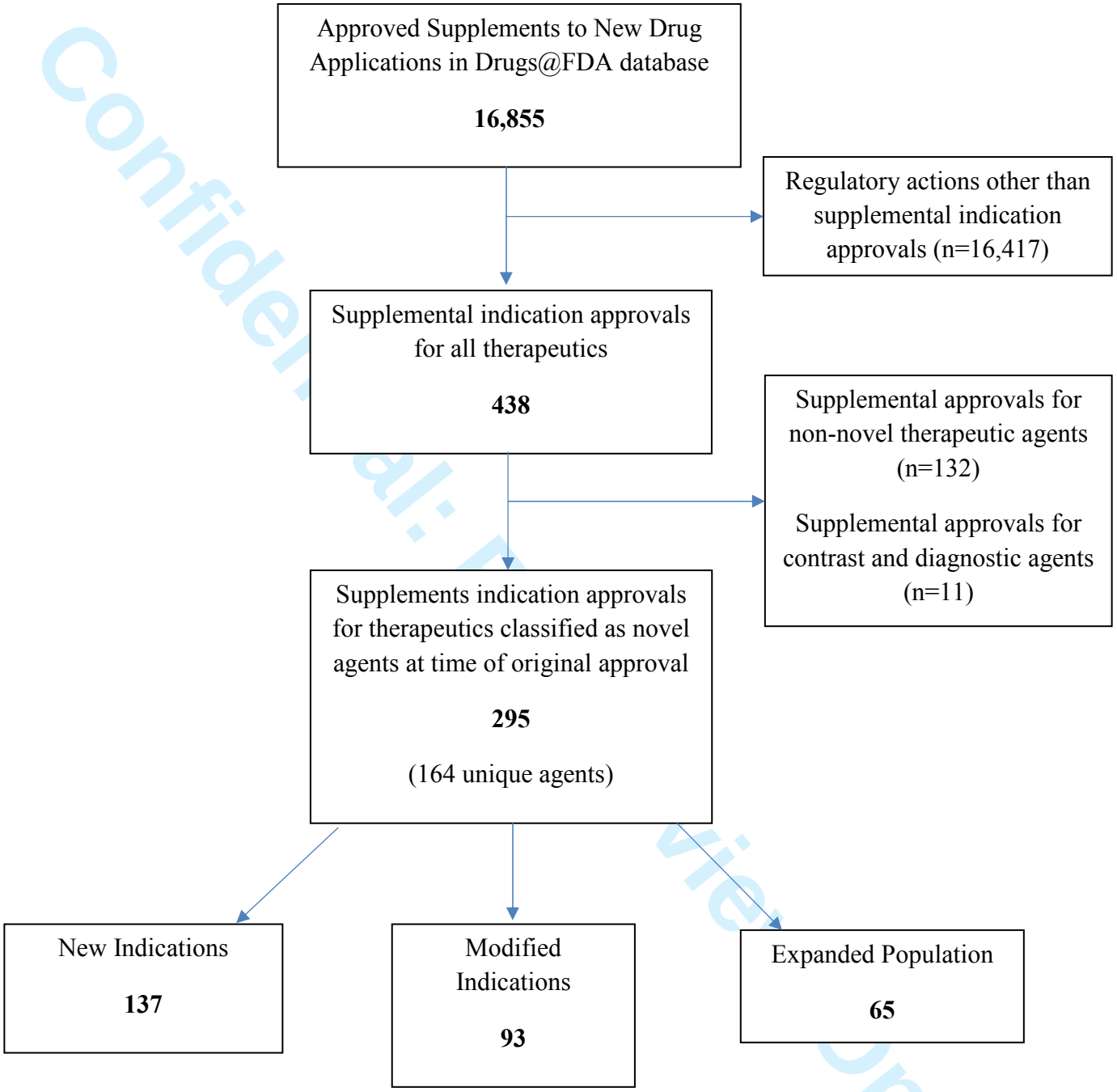
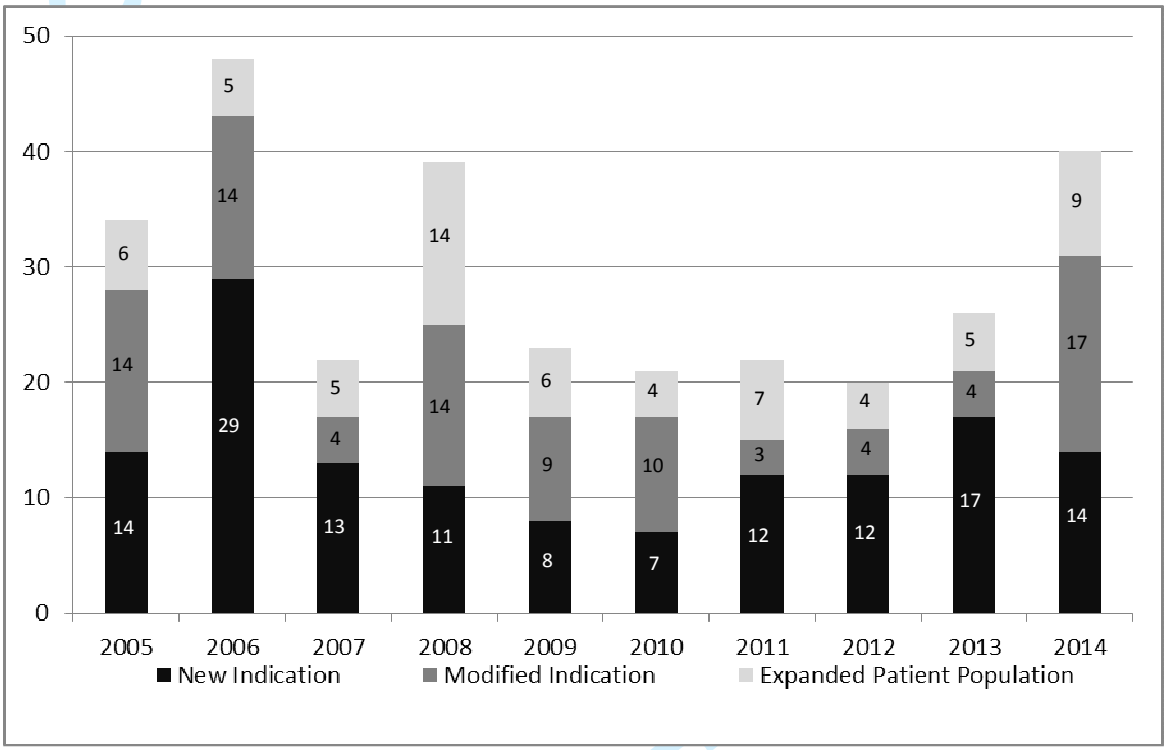


Figure 2. Supplemental Indications Approved by the FDA for Novel Therapeutic Agents, 2005-2014



Types of supplemental indications: new indication denotes no similar use was ever previously approved for the agent (*e.g.*, drug initially approved for schizophrenia, now approved for bipolar mania); modified indication denotes agent previously approved for different aspect of same indication (*e.g.*, drug initially approved for adjunctive therapy in treatment of partial-onset seizures, now indicated for use as monotherapy in this condition); expanded patient population denotes agent previously approved for same indication in different group of patients (*e.g.*, drug previously indicated for treatment of Crohn's disease in adults, now approved for use in all patients 6 years and older).

Table 1. Characteristics of Supplemental Indications for Novel Therapeutic Agents Approved by the FDA, 2005-2014

Characteristic	**N (%)***
Approval Year	
2005	34 (12)
2006	48 (16)
2007	22 (7)
2008	39 (13)
2009	23 (8)
2010	21 (7)
2011	22 (7)
2012	20 (7)
2013	26 (9)
2014	40 (14)
Supplement category	
New indication	137 (46)
Modified indication	93 (32)
Expanded population	65 (22)
Chemical type	
Small-molecule	210 (71)
Biologic	85 (29)
Therapeutic area	
Oncology	80 (27)
Infectious diseases	44 (15)
Cardiovascular disease and its risk factors**	35 (12)
Psychiatry	34 (12)
Musculoskeletal disease and rheumatology	30 (10)
Neurology	23 (8)
Gastroenterology	17 (6)
Other‡	32 (11)
Orphan drug designation	
Yes	60 (20)
No	235 (80)

*Total N=295 supplemental indications for novel therapeutic agents

**Including diabetes mellitus, hyperlipidemia, and hypertension

‡Includes allergy and pulmonology (n=7); anesthesia (n=2); dermatology (n=2); endocrinology (n=2); genitourinary medicine (n=6); hematology (n=4); ophthalmology (n=8); and transplantation medicine (n=1)

Table 2.Supplemental approvals for novel therapeutic agents approved by FDA between 2005-2014 supported by at least 1 trial with an active comparator or exclusively by trials using placebo comparators

	Trial Comparators in Efficacy Studies Supporting New Drug Approvals*					
	Active Comparator			Placebo Comparator		
Characteristic	Supplemental Approvals, (n/N, %)	Original Approvals, (n/N, %)	P value	Supplemental Approvals, (n/N, %)	Original Approvals, (n/N, %)	P value
Supplement category‡						
New indication	41/136 (30)	53/113 (47)	0.007	77/136 (57)	46/113 (41)	0.012
Modified indication	47/93 (51)	37/83 (45)	0.43	39/93 (42)	31/83 (37)	0.53
Expanded population	7/65 (11)	27/58 (47)	<0.0001	26/65 (40)	26/58 (45)	0.59
P value	<0.0001			0.03		
Chemical type						
Small-molecule	68/209 (33)	81/162 (50)	0.0007	98/209 (47)	63/162 (39)	0.12
Biologic	27/85 (32)	9/39 (23)	0.32	44/85 (52)	22/39 (56)	0.63
P value	0.90			0.45		
Therapeutic area						
Oncology	44/80 (55)	13/41 (32)	0.02	21/80 (26)	10/41 (24)	0.82
Infectious disease	21/44 (48)	31/41 (76)	0.008	9/44 (20)	9/41 (22)	0.87
Cardiovascular disease and risk factors	17/35 (49)	21/35 (60)	0.34	13/35 (37)	12/35 (34)	0.80
Psychiatry	0/34 (0)	8/13 (62)	<0.0001	33/34 (97)	5/13 (38)	<0.0001
Musculoskeletal disease and rheumatology	3/29 (10)	5/16 (31)	0.08	22/29 (76)	11/16 (69)	0.61
Neurology	1/23 (4)	0/19 (0)	0.36	18/23 (78)	19/19 (100)	0.03
Gastroenterology	3/17 (18)	6/14 (43)	0.12	8/17 (47)	6/14 (43)	0.82
Other	6/32 (19)	6/22 (27)	0.46	18/32 (56)	13/22 (59)	0.84
P value	<0.0001			<0.0001		
Orphan drug designation						
Yes	17/60 (28)	10/42 (24)	0.61	19/60 (32)	18/42 (43)	0.25
No	78/234 (33)	80/159 (50)	0.0008	123/234 (53)	67/159 (42)	0.04
P value	0.46			0.004		

*Total N=294 supplemental indications and N=201 original indications for 164 novel therapeutic agents. No active comparator information for trials supporting the supplemental approval for celecoxib (Celebrex) in July 2005 or original approval for fluvastatin (Lescol) in December 1993.

‡The supplement categories for original approvals were non-mutually exclusive. Each category included original approvals of all drugs that were subsequently approved for supplemental indications in that category.

Table 3.Supplemental approvals for novel therapeutic agents approved by FDA between 2005-2014 that were supported by at least 1 trial which used a clinical outcome as study end point, and proportion supported exclusively by trials using clinical scale or surrogate outcome as the study end point

	Trial Endpoints in Efficacy Studies Supporting New Drug Approvals*								
	Clinical Outcome			Clinical Scale			Surrogate Outcome		
Characteristic	Supplemental Approvals, (n/N, %)	Original Approvals, (n/N, %)	P value	Supplemental Approvals, (n/N, %)	Original Approvals, (n/N, %)	P value	Supplemental Approvals, (n/N, %)	Original Approvals, (n/N, %)	P value
Supplement category‡									
New indication	44/137 (32)	47/113 (42)	0.12	43/137 (31)	27/113 (24)	0.19	50/137 (36)	39/113 (35)	0.74
Modified indication	28/93 (30)	26/83 (31)	0.86	23/93 (25)	13/83 (16)	0.14	41/93 (44)	44/83 (53)	0.24
Expanded population	14/65 (22)	28/59 (47)	0.002	17/65 (26)	9/59 (15)	0.14	25/65 (38)	22/59 (37)	0.89
P value	0.29			0.50			0.51		
Chemical type									
Small-molecule	70/210 (33)	69/163 (42)	0.07	48/210 (23)	23/163 (14)	0.03	86/210 (41)	71/163 (44)	0.61
Biologic	16/85 (19)	9/39 (23)	0.58	35/85 (41)	14/39 (36)	0.58	30/85 (35)	16/39 (41)	0.54
P value	0.01			0.002			0.37		
Therapeutic area									
Oncology	24/80 (30)	9/41 (22)	0.35	0/80 (0)	0/41 (0)	1.00	56/80 (70)	32/41 (78)	0.35
Infectious disease	20/44 (45)	26/41 (63)	0.10	0/44 (0)	0/41 (0)	1.00	21/44 (48)	15/41 (37)	0.30
Cardiovascular disease and risk factors	15/35 (43)	10/36 (28)	0.18	0/35 (0)	0/36 (0)	1.00	20/35 (57)	26/36 (72)	0.18
Psychiatry	2/34 (6)	1/13 (8)	0.82	31/34 (91)	12/13 (92)	0.90	1/34 (3)	0/13 (0)	0.53
Musculoskeletal disease and rheumatology	1/30 (3)	2/16 (13)	0.23	23/30 (77)	10/16 (63)	0.31	5/30 (17)	4/16 (25)	0.50
Neurology	11/23 (48)	13/19 (68)	0.18	10/23 (43)	6/19 (32)	0.43	1/23 (4)	0/19 (0)	0.36
Gastroenterology	6/17 (35)	11/14 (79)	0.02	9/17 (53)	2/14 (14)	0.03	0/17 (0)	1/14 (7)	0.26
Other	7/32 (22)	6/22 (27)	0.65	10/32 (31)	7/22 (32)	0.96	12/32 (38)	9/22 (41)	0.80
P value	<0.0001			<0.0001			<0.0001		
Orphan drug designation									
Yes	11/60 (18)	13/42 (31)	0.14	12/60 (20)	3/42 (7)	0.07	34/60 (57)	26/42 (62)	0.60
No	75/235 (32)	65/160 (41)	0.08	71/235 (30)	34/160 (21)	0.048	82/235 (35)	61/160 (38)	0.51
P value	0.04			0.12			0.002		

*Total N=295 supplemental indications and N=202 original indications for 164 novel therapeutic agents.

‡The supplement categories for original approvals were non-mutually exclusive. Each category included original approvals of all drugs that were subsequently approved for supplemental indications in that category.

Appendix Table 1. Detailed Characteristics of Supplemental Indications for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2005-2014

Generic Name*	Brand Name	Supplemental Indication	sNDA Year	Supplement Category	Chemical Type	Therapeutic Area	Orphan Drug Designation
Dabrafenib mesylate	Tafinlar	Use in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test	2014	Modified Indication	Small-molecule	Oncology	Y
Trametinib dimethyl sulfoxide	Mekinist	Use in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test	2014	Modified Indication	Small-molecule	Oncology	Y
Ecallantide	Kalbitor	Broaden the age range for the hereditary angioedema indication to patients 12 years of age and older	2014	Expanded patient population	Biologic	Allergy and Pulmonology	Y
Ivacaftor	Kalydeco	Treatment of Cystic Fibrosis patients age 6 years and older who have mutations in the CFTR gene [in addition to the G551D mutation]	2014	Modified Indication	Small-molecule	Allergy and Pulmonology	Y
Topiramate	Topamax	Prophylaxis of migraine headache in adolescents 12 years of age and older	2014	Expanded patient population	Small-molecule	Neurology	N
Entecavir	Baraclude	Expand the patient population for treatment to include pediatric subjects two years of age and older with chronic hepatitis B virus infection	2014	Expanded patient population	Small-molecule	Infectious Disease	N
Omalizumab	Xolair	Treatment of Chronic Idiopathic Urticaria	2014	New Indication	Biologic	Allergy and Pulmonology	N

Apixaban	Eliquis	Prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE), in adult patients who have undergone hip or knee replacement surgery	2014	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Dabigatran (1)	Pradaxa	Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days	2014	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Dabigatran (2)	Pradaxa	Reduce the risk of recurrence of DVT and PE in patients who have been previously treated	2014	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Ofatumumab	Arzerra	Use in combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-based therapy is considered inappropriate	2014	Modified Indication	Biologic	Oncology	Y
Palonosetron	Aloxi	Prevention of nausea and vomiting associated with cancer chemotherapy in pediatric patients 1 month and older	2014	Expanded patient population	Small-molecule	Gastroenterology	N
Panitumumab (1)	Vectibix	First-line treatment, in combination with FOLFOX, of patients with wild-type KRAS (exon 2 in codons 12 or 13) metastatic colorectal cancer (mCRC), as determined by an FDA-approved test for this use	2014	Modified Indication	Biologic	Oncology	N
Panitumumab (2)	Vectibix	Treatment of patients with wild-type KRAS (exon 2 in codons 12 or 13) metastatic colorectal cancer (mCRC), as determined by an FDA-approved test for this use, following disease progression on fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens	2014	Modified Indication	Biologic	Oncology	N
Aflibercept	Eylea	Treatment of Diabetic Macular Edema	2014	New	Biologic	Ophthalmology	N

				Indication			
Ibrutinib	Imbruvica	Treatment of patients with chronic lymphocytic leukemia with 17p deletion	2014	Modified Indication	Small-molecule	Oncology	Y
Lacosamide	Vimpat	Use as monotherapy (conversion to and initial) in the treatment of partial-onset seizures in patients with epilepsy age 17 years and older	2014	Modified Indication	Small-molecule	Neurology	N
Eltrombopag olamine	Promacta	Treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy	2014	New Indication	Small-molecule	Hematology	Y
Bevacizumab	Avastin	Treatment of persistent, recurrent, or metastatic carcinoma of the cervix	2014	New Indication	Biologic	Oncology	N
Alglucosidase alfa	Lumizyme	Extend the population to all patients with Pompe disease (acid α-glucosidase (GAA) deficiency), including infantile-onset and late-onset patients less than 8 years of age	2014	Expanded patient population	Biologic	Musculoskeletal disease and rheumatology	Y
Apixaban (1)	Eliquis	Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE)	2014	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Apixaban (2)	Eliquis	Reduction in the risk of recurrent DVT and PE following initial therapy	2014	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Methylnaltrexone bromide	Relistor	Expand the currently approved indication to include the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain	2014	Modified Indication	Small-molecule	Gastroenterology	N
Adalimumab (1)	Humira	Expand the patient population to include pediatric Crohn's disease patients aged 6 years or older	2014	Expanded patient population	Biologic	Gastroenterology	Y
Adalimumab (2)	Humira	Treatment of Polyarticular Juvenile Idiopathic Arthritis (pJIA) in patients 2 to less than 4 years of age	2014	Expanded patient population	Biologic	Musculoskeletal disease and rheumatology	Y

Enzalutamide	Xtandi	Treatment of chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (mCRPC)	2014	Modified Indication	Small-molecule	Oncology	N
Duloxetine	Cymbalta	Treatment of general anxiety disorder for children and adolescents ages 7-17	2014	Expanded patient population	Small-molecule	Psychiatry	N
Bortezomib	Velcade	Treatment of patients with mantle cell lymphoma [without requirement for receiving at least 1 prior therapy]	2014	Modified Indication	Small-molecule	Oncology	Y
Aflibercept	Eylea	Treatment of macular edema following Branch Retinal Vein Occlusion (BRVO)	2014	Modified Indication	Biologic	Ophthalmology	N
Rifapentine	Priftin	Treatment of latent tuberculosis infection (LTBI) caused by Mycobacterium tuberculosis in combination with isoniazid (INH) in patients ≥2 years at high risk of progression to tuberculosis disease	2014	Modified Indication	Small-molecule	Infectious Disease	Y
Cinacalcet	Sensipar	Hypercalcemia in adult patients with primary hyperparathyroidism for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy	2014	Modified Indication	Small-molecule	Endocrinology	Y
Bevacizumab	Avastin	Use in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for the treatment of patients with platinum-resistant, recurrent, epithelial ovarian, fallopian tube, or primary peritoneal cancer, who received no more than two prior chemotherapy regimens	2014	New Indication	Biologic	Oncology	N
Ramucirumab	Cyramza	Treatment, in combination with paclitaxel, of patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine or platinum-containing	2014	Modified Indication	Biologic	Oncology	Y

		chemotherapy					
Aripiprazole	Abilify	Use in pediatric patients with Tourette's Disorder	2014	New Indication	Small-molecule	Psychiatry	N
Denosumab	Xgeva	Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy	2014	New Indication	Biologic	Musculoskeletal disease and rheumatology	N
Ruxolitinib phosphate	Jakafi	Treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea	2014	New Indication	Small-molecule	Oncology	Y
Cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate	Stribild	Treatment of HIV/AIDS in patients who are virologically-suppressed (HIV-q RNA<50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure in order to replace their current regimen	2014	Modified Indication	Small-molecule	Infectious Disease	N
Lanreotide acetate	Somatuline Depot	Treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival	2014	New Indication	Small-molecule	Oncology	Y
Spinosad	Natroba	Modification of the indication to include patients 6 months of age and older with head lice infestation	2014	Expanded patient population	Small-molecule	Dermatology	N
Ivacaftor	Kalydeco	Treatment of cystic fibrosis in patients 6 years and older who have the R 117H mutation in the CF transmembrane conductance regulator (CFTR) gene	2014	Modified Indication	Small-molecule	Allergy and Pulmonology	Y
Deferasirox	Exjade	Treatment of chronic iron overload in patients 10 years of age and older with non-transfusion dependent thalassemia (NTDT) syndromes and with a liver iron concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw) and serum ferritin greater than 300	2013	New Indication	Small-molecule	Hematology	Y

		mcg/L.					
Bevacizumab	Avastin	Second line treatment, in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy, of patients with metastatic colorectal carcinoma who have progressed on a first-line Avastin-containing regimen	2013	Modified Indication	Biologic	Oncology	N
OnabotulinumtoxinA	Botox	Treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adults who have had an inadequate response to or are intolerant of an anticholinergic medication	2013	New Indication	Biologic	Genitourinary	Y
Imatinib mesylate	Gleevec	Treatment of pediatric patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy	2013	Expanded patient population	Small-molecule	Oncology	Y
Boceprevir	Victrelis	Treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients (18 years of age or older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy	2013	Modified Indication	Small-molecule	Infectious Disease	N
Lubiprostone	Amitiza	Treatment of opioid-induced constipation (OIC) in adults with chronic, non-cancer pain	2013	New Indication	Small-molecule	Gastroenterology	N
Tocilizumab	Actemra	Treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older	2013	New Indication	Biologic	Musculoskeletal disease and rheumatology	N
Erlotinib	Tarceva	First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-	2013	Modified Indication	Small-molecule	Oncology	N

		approved test					
Golimumab	Simponi	Adult patients with moderately to severely active ulcerative colitis who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine	2013	New Indication	Biologic	Gastroenterology	N
Canakinumab	Ilaris	Treatment of Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older	2013	New Indication	Biologic	Musculoskeletal disease and rheumatology	Y
Lenalidomide	Revlimid	Patients with Mantle Cell Lymphoma whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib	2013	New Indication	Small-molecule	Oncology	Y
Telavancin	Vibativ	Treatment of hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of Staphylococcus aureus (including methicillin-susceptible and resistant isolates) when alternative treatments are not suitable	2013	New Indication	Small-molecule	Infectious Disease	N
Denosumab	Xgeva	Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity	2013	New Indication	Biologic	Oncology	N
Lurasidone (1)	Latuda	Treatment of patients with depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy	2013	New Indication	Small-molecule	Psychiatry	N
Lurasidone (2)	Latuda	Treatment of patients with depressive episodes associated with bipolar I disorder (bipolar depression) as adjunctive therapy with lithium or valproate	2013	New Indication	Small-molecule	Psychiatry	N
Fluoxetine	Prozac	Use in combination with olanzapine for treatment of depressive episodes associated with bipolar I	2013	Expanded patient	Small-molecule	Psychiatry	N

		disorder in patients 10-17 years of age		population			
Olanzapine	Zyprexa	Use in combination with fluoxetine for treatment of depressive episodes associated with bipolar I disorder in patients 10-17 years of age	2013	Expanded patient population	Small-molecule	Psychiatry	N
OnabotulinumtoxinA	Botox Cosmetic	Temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients	2013	New Indication	Biologic	Dermatology	N
Certolizumab pegol	Cimzia	Treatment of adult patients with active psoriatic arthritis	2013	New Indication	Biologic	Musculoskeletal disease and rheumatology	N
Ustekinumab	Stelara	Treatment of active psoriatic arthritis, alone or in combination with methotrexate	2013	New Indication	Biologic	Musculoskeletal disease and rheumatology	N
Pertuzumab	Perjeta	Use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer	2013	Modified Indication	Biologic	Oncology	N
Vigabatrin	Sabril	Adjunctive therapy in children 10-16 years of age with refractory complex partial seizures	2013	Expanded patient population	Small-molecule	Neurology	N
Certolizumab pegol	Cimzia	Treatment of adult patients with active ankylosing spondylitis	2013	New Indication	Biologic	Musculoskeletal disease and rheumatology	N
Sorafenib tosylate	Nexavar	Treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment	2013	New Indication	Small-molecule	Oncology	Y
Collagenase clostridium	Xiaflex	Treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of	2013	New	Biologic	Genitourinary	Y

histolyticum		at least 30 degrees		Indication			
Raltegravir potassium	Isentress	Treatment of HIV-1 infection in pediatric patients 4 weeks of age and older, weighing at least 3 kg to less than 20 kg	2013	Expanded patient population	Small-molecule	Infectious Disease	N
Tenofovir disoproxil fumarate	Viread	Use in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients 2 to less than 12 years of age, weighing greater than or equal to 17 kg, who can swallow an intact tablet.	2012	Expanded patient population	Small-molecule	Infectious Disease	N
Lisdexamfetamine dimesylate	Vyvanse	Maintenance treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults	2012	Modified Indication	Small-molecule	Psychiatry	N
Montelukast	Singulair	Prevention of exercise-induced bronchoconstriction (EIB) in patients 6 to 14 years of age	2012	Expanded patient population	Small-molecule	Allergy and Pulmonology	N
Etravirine	Intelence	Treatment of HIV-1 infection, in treatment-experienced pediatric patients 6 years to less than 18 years of age in combination with other antiretroviral agents	2012	Expanded patient population	Small-molecule	Infectious Disease	N
Pazopanib	Votrient	Treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy	2012	New Indication	Small-molecule	Oncology	N
Insulin determir recombinant	Levemir	Use in combination with liraglutide for treatment of diabetes	2012	Modified Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Pregabalin	Lyrica	Management of neuropathic pain associated with spinal cord injury	2012	New Indication	Small-molecule	Neurology	N
Difluprednate	Durezol	Treatment of endogenous anterior uveitis	2012	New Indication	Small-molecule	Ophthalmology	N
Gabapentin enacarbil	Horizant	Management of postherpetic neuralgia	2012	New Indication	Small-molecule	Neurology	N

Everolimus	Afinitor	Treatment of postmenopausal women with advanced hormone receptor-positive, HER-2 negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole	2012	New Indication	Small-molecule	Oncology	N
Cetuximab	Erbitux	Use in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment of K-Ras mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer	2012	Modified Indication	Biologic	Oncology	N
Ranibizumab	Lucentis	Treatment of patients with diabetic macular edema	2012	New Indication	Biologic	Ophthalmology	N
Adalimumab	Humira	Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine	2012	New Indication	Biologic	Gastroenterology	Y
Denosumab	Prolia	Treatment to increase bone mass in men with osteoporosis at high risk of fracture	2012	New Indication	Biologic	Musculoskeletal disease and rheumatology	N
Aflibercept	Eylea	Treatment of macular edema following Central Retinal Vein Occlusion (CRVO)	2012	New Indication	Biologic	Ophthalmology	N
Eltrombopag olamine	Promacta	Treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy	2012	New Indication	Small-molecule	Infectious Disease	Y
Rivaroxaban	Xarelto	Treatment and reduction in risk for pulmonary embolism and deep vein thrombosis	2012	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Abiraterone	Zytiga	Use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer [removed requirement of receiving prior chemotherapy containing docetaxel]	2012	Modified Indication	Small-molecule	Oncology	N

Oseltamivir	Tamiflu	Treatment of influenza in patients 2 weeks to one year of age	2012	Expanded patient population	Small-molecule	Infectious Disease	N
Anakinra	Kineret	Treatment of Neonatal Onset Multi-system Inflammatory Disease (NOMID)	2012	New Indication	Biologic	Musculoskeletal disease and rheumatology	N
Rituximab	Rituxan	Use as single-agent maintenance therapy in patients with previously untreated follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL) who achieve a response to Rituxan in combination with chemotherapy	2011	Modified Indication	Biologic	Oncology	Y
Cinacalcet	Sensipar	Treatment of severe hypercalcemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy	2011	New Indication	Small-molecule	Endocrinology	Y
Aripiprazole	Abilify	Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate	2011	Modified Indication	Small-molecule	Psychiatry	N
Peginterferon alfa-2b	Sylatron	Adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy	2011	New Indication	Biologic	Oncology	N
Rituximab	Rituxan	Use in combination with glucocorticoids for the treatment of patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)	2011	New Indication	Biologic	Musculoskeletal disease and rheumatology	Y
Tocilizumab	Actemra	Treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older	2011	New Indication	Biologic	Musculoskeletal disease and rheumatology	N
Sunitinib malate	Sutent	Treatment of progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable, locally advanced, or metastatic disease	2011	New Indication	Small-molecule	Oncology	N

Everolimus	Afinitor	Treatment of patients with progressive neuroendocrine tumors of pancreatic origin (PNET) that are unresectable, locally advanced, or metastatic	2011	New Indication	Small-molecule	Oncology	N
Insulin lispro recombinant	Humalog	Pediatric use of Humalog in a continuous insulin infusion pump for treatment of type 1 diabetes	2011	Expanded patient population	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Romidepsin	Istodax	Treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy	2011	New Indication	Small-molecule	Oncology	Y
Topiramate	Topamax	Expansion of the initial monotherapy indication for Topamax (topiramate) in patients down to 2 years of age with partial onset or primary generalized tonic-clonic seizures	2011	Expanded patient population	Small-molecule	Neurology	N
OnabotulinumtoxinA	Botox	Treatment of adults with urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis) who have an inadequate response to or are intolerant of an anticholinergic medication	2011	New Indication	Biologic	Genitourinary	Y
Peginterferon alfa-2a (1)	Pegasys	Treatment of chronic hepatitis C patients with renal impairment (creatinine clearance less than 50 mL/min), including those who are receiving chronic hemodialysis	2011	Expanded patient population	Biologic	Infectious Disease	N
Peginterferon alfa-2a (2)	Pegasys	Treatment of chronic hepatitis C in combination with Copegus in patients 5 to 17 years of age	2011	Expanded patient population	Biologic	Infectious Disease	N
Infliximab	Remicade	Treatment of pediatric ulcerative colitis	2011	Expanded patient population	Biologic	Gastroenterology	N
Denosumab (1)	Prolia	Treatment to increase bone mass in women at high risk for fracture receiving adjuvant	2011	New Indication	Biologic	Musculoskeletal disease and	N

		aromatase inhibitor therapy for breast cancer				rheumatology	
Denosumab (2)	Prolia	Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer	2011	New Indication	Biologic	Musculoskeletal disease and rheumatology	N
Tadalafil (1)	Cialis	Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)	2011	New Indication	Small-molecule	Genitourinary	N
Tadalafil (2)	Cialis	Treatment of erectile dysfunction (ED) and the signs and symptoms of BPH	2011	New Indication	Small-molecule	Genitourinary	N
Cetuximab	Erbitux	First-line treatment of patients with recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU	2011	Modified Indication	Biologic	Oncology	N
Raltegravir potassium	Isentress	Use in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients 6 to 18 years of age	2011	Expanded patient population	Small-molecule	Infectious Disease	N
Levetiracetam	Keppra	Use as adjunctive therapy in the treatment of partial onset seizures in children 1 month to less than 4 years	2011	Expanded patient population	Small-molecule	Neurology	N
Lapatinib ditosylate	Tykerb	Use in combination with letrozole tablets for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated	2010	Modified Indication	Small-molecule	Oncology	N
Olmesartan medoxomil	Benicar	Treatment of hypertension in pediatric patients 6 to 16 years of age	2010	Expanded patient population	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Rituximab (1)	Rituxan	Treatment of patients previously treated for CD20-positive chronic lymphocytic leukemia (CLL) in combination with fludarabine and cyclophosphamide (FC)	2010	New Indication	Biologic	Oncology	Y

Rituximab (2)	Rituxan	Treatment of patients previously untreated for CD20-positive chronic lymphocytic leukemia (CLL) in combination with fludarabine and cyclophosphamide (FC) has been approved	2010	New Indication	Biologic	Oncology	Y
Sitagliptin (1)	Januvia	Use in combination with metformin and a PPARγ agonist as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus who are inadequately controlled on combination therapy with metformin and a PPARγ agonist	2010	Modified Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Sitagliptin (2)	Januvia	Use as combination therapy with a PPARγ agonist for type 2 diabetes mellitus	2010	Modified Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Sitagliptin (3)	Januvia	Use in combination with insulin, alone or in combination with metformin for type 2 diabetes mellitus	2010	Modified Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
OnabotulinumtoxinA	Botox	Treatment of upper limb spasticity	2010	New Indication	Biologic	Neurology	Y
Tenofovir disoproxil fumarate	Viread	Expand the indication to include the treatment of HIV infection in combination with other antiretroviral agents in patients 12 to less than 18 years of age	2010	Expanded patient population	Small-molecule	Infectious Disease	N
Erlotinib	Tarceva	Maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy	2010	Modified Indication	Small-molecule	Oncology	Y
Maraviroc	Selzentry	Expand the patient population [use in combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1] to include patients with renal impairment	2010	Expanded patient population	Small-molecule	Infectious Disease	N
Nilotinib	Tasigna	Treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase	2010	Modified Indication	Small-molecule	Oncology	Y

Ranibizumab	Lucentis	Treatment of macular edema following retinal vein occlusion (RVO)	2010	New Indication	Biologic	Ophthalmology	N
Travoprost	Travatan	Reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension	2010	Modified Indication	Small-molecule	Ophthalmology	N
Asenapine (1)	Saphris (1)	Maintenance treatment of schizophrenia in adults	2010	Modified Indication	Small-molecule	Psychiatry	N
Asenapine (2)	Saphris (2)	Adjunctive therapy with either lithium or valproate for the acute treatment of manic or mixed episodes associated with bipolar I disorder	2010	Modified Indication	Small-molecule	Psychiatry	N
Dasatinib	Sprycel	Treatment of newly diagnosed adults with chronic myeloid leukemia (CML) in chronic phase	2010	Modified Indication	Small-molecule	Oncology	Y
Everolimus	Afinitor	Treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection	2010	New Indication	Small-molecule	Oncology	N
OnabotulinumtoxinA	Botox	Prophylaxis of headaches in adults with chronic migraine	2010	New Indication	Biologic	Neurology	Y
Trastuzumab	Herceptin	Treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease	2010	New Indication	Biologic	Oncology	N
Lisdexamfetamine dimesylate	Vyvanse	Treatment of ADHD in adolescent patients ages 13 to 17	2010	Expanded patient population	Small-molecule	Psychiatry	N
Glatiramer acetate	Copaxone	Reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI	2009	Modified Indication	Small-molecule	Neurology	Y

		features consistent with multiple sclerosis					
Tigecycline	Tygacil	Treatment of community acquired bacterial pneumonia	2009	New Indication	Small-molecule	Infectious Disease	N
Peginterferon alfa-2b	Pegintron	Retreatment of chronic hepatitis C patients who failed to respond or relapsed after treatment with combination alpha intereron/ribavirin therapy	2009	Modified Indication	Biologic	Infectious Disease	N
Bevacizumab	Avastin	Treatment of glioblastoma with progressive disease following prior therapy	2009	New Indication	Biologic	Oncology	N
Certolizumab pegol	Cimzia	Treatment of adults with moderately to severely active rheumatoid arthritis	2009	New Indication	Biologic	Musculoskeletal disease and rheumatology	N
Pemetrexed disodium	Alimta	Maintenance treatment in patients with advanced or metastatic nonsquamous non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first line chemotherapy	2009	Modified Indication	Small-molecule	Oncology	Y
Raltegravir potassium	Isentress	Use in combination with other antiretrovirals for the treatment of HIV-1 infection in treatment-naive adult patients	2009	Modified Indication	Small-molecule	Infectious Disease	N
Bevacizumab	Avastin	Treatment of metastatic renal cell carcinoma in combination with interferon alfa	2009	New Indication	Biologic	Oncology	N
Bosentan	Tracleer	Treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class II to IV symptoms to improve exercise capacity and decrease clinical worsening	2009	Modified Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	Y
Ibritumomab tiuxetan	Zevalin	Treatment of previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy	2009	Modified Indication	Biologic	Oncology	Y

Telmisartan	Micardis	Reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors	2009	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Cardesartan cilexetil	Atacand	Treatment of hypertension in children 1 to <17 years of age	2009	Expanded patient population	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Colesevelam	Welchol	Reduction of LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia as monotherapy or in combination with a statin after failing an adequate trial of diet therapy	2009	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Rosuvastatin	Crestor	Treatment of heterozygous familial hypercholesterolemia in adolescent boys and postmenarchal girls, ages 10 to 17 years	2009	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Ziprasidone	Geodon	Maintenance treatment of bipolar disorder, as an adjunct to lithium or valproate	2009	Modified Indication	Small-molecule	Psychiatry	N
Duloxetine	Cymbalta	Maintenance of Generalized Anxiety Disorder (GAD)	2009	Modified Indication	Small-molecule	Psychiatry	N
Aripiprazole	Abilify	Treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years)	2009	New Indication	Small-molecule	Psychiatry	N
Pantoprazole	Protonix	Short term treatment of erosive esophagitis associated with GERD in pediatric patients ages five years and older	2009	Expanded patient population	Small-molecule	Gastroenterology	N
Maraviroc	Selzentry	Treatment of therapy-naïve adults infected with CCR5-tropic HIV-1 virus in combination with other antiretroviral agents	2009	Modified Indication	Small-molecule	Infectious Disease	N
Olanzapine (1)	Zyprexa	Treatment of manic or mixed episodes of bipolar I disorder in adolescents	2009	Expanded patient population	Small-molecule	Psychiatry	N

Olanzapine (2)	Zyprexa	Treatment of schizophrenia in adolescents	2009	Expanded patient population	Small-molecule	Psychiatry	N
Quetiapine fumarate (1)	Seroquel	Treatment of schizophrenia in adolescents 13 to 17 years of age	2009	Expanded patient population	Small-molecule	Psychiatry	N
Quetiapine fumarate (2)	Seroquel	Treatment of bipolar mania in children and adolescents 10 to 17 years of age	2009	Expanded patient population	Small-molecule	Psychiatry	N
Colesevelam	Welchol	Use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	2008	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Micafungin	Mycamine	Treatment of patients with candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses	2008	New Indication	Small-molecule	Infectious Disease	N
Eplerenone	Inspra	Treatment of hypertension in pediatric patients	2008	Expanded patient population	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Rituximab	Rituxan	Expanding the indication to include a claim to slow the progression of structural damage [in adult patients with moderately- to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies]	2008	Modified Indication	Biologic	Musculoskeletal disease and rheumatology	Y
Trastuzumab	Herceptin	Use as a single agent, for the adjuvant treatment of HER2-overexpressing node-negative (ER/PR negative or with one high-risk feature) or node-positive breast cancer, following multi-modality anthracycline based therapy	2008	Modified Indication	Biologic	Oncology	N
Adalimumab	Humira	Treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy,	2008	New Indication	Biologic	Musculoskeletal disease and rheumatology	Y

		and when other systemic therapies are medically less appropriate					
Palonosetron	Aloxi	Prevention of postoperative nausea and vomiting for up to 24 hours following surgery	2008	New Indication	Small-molecule	Gastroenterology	N
Aripiprazole	Abilify	Treatment of acute manic or mixed episodes associated with Bipolar I Disorder in pediatric patients aged 10 to 17 years	2008	Expanded patient population	Small-molecule	Psychiatry	N
Adalimumab	Humira	Treatment of Juvenile Idiopathic Arthritis	2008	New Indication	Biologic	Musculoskeletal disease and rheumatology	Y
Bevacizumab	Avastin	Use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast cancer	2008	New Indication	Biologic	Oncology	N
Insulin aspart recombinant	Novolog	Pediatric pump use for diabetes mellitus	2008	Expanded patient population	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Atazanavir	Reyataz	Treatment of HIV-1 infection in pediatric patients (ages 6 to 18 years of age)	2008	Expanded patient population	Small-molecule	Infectious Disease	N
Lubiprostone	Amitiza	Treatment of Irritable Bowel Syndrome with constipation in women ≥18 years old	2008	New Indication	Small-molecule	Gastroenterology	N
Lisdexamfetamine dimesylate	Vyvanse	Treatment of attention deficit hyperactivity disorder in the adult population	2008	Expanded patient population	Small-molecule	Psychiatry	N
Abatacept	Orencia	Treatment of moderate to severe polyarticular juvenile idiopathic arthritis (JIA)	2008	New Indication	Biologic	Musculoskeletal disease and rheumatology	N

Argatroban	Acova	Use in certain pediatric patients with Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia with Thrombosis (HITTS)	2008	Expanded patient population	Small-molecule	Hematology	N
Quetiapine fumarate	Seroquel	Maintenance treatment for bipolar I disorder, as adjunctive therapy to lithium or divalproex	2008	Modified Indication	Small-molecule	Psychiatry	N
Atomoxetine	Strattera	Maintenance treatment of attention-deficit hyperactivity disorder (ADHD) in children and adolescents	2008	Modified Indication	Small-molecule	Psychiatry	N
Aripiprazole (1)	Abilify	Use as monotherapy in the acute treatment of bipolar disorder, manic or mixed	2008	Modified Indication	Small-molecule	Psychiatry	N
Aripiprazole (2)	Abilify	Use as adjunctive therapy added to lithium or valproate in the short-term treatment of bipolar disorder, manic or mixed	2008	Modified Indication	Small-molecule	Psychiatry	N
Trastuzumab (1)	Herceptin	Use as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel, for the adjuvant treatment of patients with HER2-overexpressing, node-positive or high-risk node-negative, breast cancer	2008	Modified Indication	Biologic	Oncology	N
Trastuzumab (2)	Herceptin	Use as part of a treatment regimen containing docetaxel and carboplatin, for the adjuvant treatment of HER2 over-expressing, node-positive or high-risk node-negative, breast cancer	2008	Modified Indication	Biologic	Oncology	N
Dutasteride	Avodart	Use in combination with tamsulosin for the treatment of symptomatic Benign Prostatic Hyperplasia (BPH)	2008	Modified Indication	Small-molecule	Genitourinary	N
Bortezomib	Velcade	Treatment of patients with multiple myeloma [removed requirement for at least 1 prior therapy]	2008	Modified Indication	Small-molecule	Oncology	Y
Tipranavir	Aptivus	Co-administered with ritonavir, for combination antiretroviral treatment of HIV-1 infected pediatric (age 2 to 18 years) patients who are treatment-experienced and infected with HIV-1	2008	Expanded patient population	Small-molecule	Infectious Disease	N

		strains resistant to more than one protease inhibitor					
Rabeprazole	Aciphex	Short-term treatment of symptomatic GERD in adolescent patients 12 years of age and above	2008	Expanded patient population	Small-molecule	Gastroenterology	N
Atomoxetine	Strattera	Use in patients with attention-deficit hyperactivity disorder (ADHD) and comorbid anxiety disorder without causing worsening of anxiety	2008	Modified Indication	Small-molecule	Psychiatry	N
Caspofungin (1)	Cancidas	In pediatric patients (3 months to 16 years of age), empirical therapy for presumed fungal infections in febrile, neutropenic patients	2008	Expanded patient population	Small-molecule	Infectious Disease	N
Caspofungin (2)	Cancidas	In pediatric patients (3 months to 16 years of age), treatment of Candidemia and the following Candida infections: intra-abdominal abscesses, peritonitis and pleural space infections	2008	Expanded patient population	Small-molecule	Infectious Disease	N
Caspofungin (3)	Cancidas	In pediatric patients (3 months to 16 years of age), treatment of Esophageal Candidiasis	2008	Expanded patient population	Small-molecule	Infectious Disease	N
Caspofungin (4)	Cancidas	In pediatric patients (3 months to 16 years of age), treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole)	2008	Expanded patient population	Small-molecule	Infectious Disease	N
Tenofovir disoproxil fumarate	Viread	Treatment of Chronic Hepatitis B	2008	New Indication	Small-molecule	Infectious Disease	N
Rocuronium bromide	Zemuron	Use in pediatric patients as adjunct to general anesthesia	2008	Expanded patient population	Small-molecule	Anesthesia	N

Pemetrexed disodium (1)	Alimta	Use in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer	2008	Modified Indication	Small-molecule	Oncology	Y
Pemetrexed disodium (2)	Alimta	Use as a single-agent for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy	2008	Modified Indication	Small-molecule	Oncology	Y
Darunavir ethanolate	Prezista	Treatment of human immunodeficiency virus (HIV) in antiretroviral treatment-naïve adults	2008	Modified Indication	Small-molecule	Infectious Disease	N
Dexmedetomidine	Precedex	Sedation of non-intubated patients prior to and/or during surgical and other procedures	2008	New Indication	Small-molecule	Anesthesia	N
Insulin glulisine recombinant	Apidra	Use in patients 4 through 17 years old with diabetes mellitus	2008	Expanded patient population	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Rosuvastatin	Crestor	Treatment of patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipoproteinemia) as an adjunct to diet	2008	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Duloxetine	Cymbalta	Treatment of Generalized Anxiety Disorder (GAD)	2007	New Indication	Small-molecule	Psychiatry	N
Adalimumab	Humira	Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab	2007	New Indication	Biologic	Gastroenterology	Y
Atorvastatin	Lipitor	Use in adult patients with clinically evident coronary heart disease to reduce the risk of non-fatal myocardial infarction, fatal and non-fatal stroke, angina, revascularization procedures, and	2007	Modified Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N

		hospitalization for congestive heart failure					
Levetiracetam	Keppra	Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy	2007	New Indication	Small-molecule	Neurology	N
Zolpidem	Ambien	Treatment of Attention-Deficit-Hyperactivity-Disorder-associated insomnia in the pediatric population (ages ≥6 years old to ≤17 years old)	2007	New Indication	Small-molecule	Psychiatry	N
Montelukast	Singulair	Prevention of exercise-induced bronchoconstriction in patients 15 years of age and older	2007	New Indication	Small-molecule	Allergy and Pulmonology	N
Dalteparin	Fragmin	Extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to reduce the recurrence of VTE in patients with cancer	2007	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Tinidazole	Tindamax	Treatment of bacterial vaginosis in non-pregnant females	2007	New Indication	Small-molecule	Infectious Disease	N
Pregabalin	Lyrica	Management of fibromyalgia	2007	New Indication	Small-molecule	Neurology	N
Risperidone (1)	Risperdal	Treatment of schizophrenia in adolescents (ages 13-17)	2007	Expanded patient population	Small-molecule	Psychiatry	N
Risperidone (2)	Risperdal	Treatment of bipolar I disorder in children (ages 10-12) and adolescents (ages 13-17)	2007	Expanded patient population	Small-molecule	Psychiatry	N
Docetaxel	Taxotere	Use in combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [removes inoperable requirement]	2007	Modified Indication	Small-molecule	Oncology	N

Raloxifene (1)	Evista	Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis	2007	New Indication	Small-molecule	Oncology	N
Raloxifene (2)	Evista	Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer	2007	New Indication	Small-molecule	Oncology	N
Alemtuzumab	Campath	Use as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)	2007	Modified Indication	Biologic	Oncology	Y
Aripiprazole	Abilify	Treatment of schizophrenia in adolescents aged 13-17	2007	Expanded patient population	Small-molecule	Psychiatry	N
Cetuximab	Erbitux	Expand the colorectal cancer indication to include cetuximab as a single agent in patients with EGFR-expressing, metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens	2007	Modified Indication	Biologic	Oncology	N
Rosuvastatin	Crestor	Adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels	2007	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Aripiprazole	Abilify	Use as an adjunctive treatment to treat patients with major depressive disorder	2007	New Indication	Small-molecule	Psychiatry	N
Sorafenib tosylate	Nexavar	Treatment of unresectable hepatocellular carcinoma	2007	New Indication	Small-molecule	Oncology	Y
Valsartan	Diovan	Treatment of hypertension in pediatric patients 6-16 years of age	2007	Expanded patient population	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Adefovir dipivoxil	Hepsera	Treatment of chronic hepatitis B in pediatric patients (ages 12 to 17 years)	2007	Expanded patient population	Small-molecule	Infectious Disease	N

Rituximab	Rituxan	Use in combination with methotrexate to reduce the signs and symptoms in adult patients with moderately- to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies	2006	New Indication	Biologic	Musculoskeletal disease and rheumatology	Y
Docetaxel	Taxotere	Use in combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease	2006	New Indication	Small-molecule	Oncology	N
Zanamivir	Relenza	Prophylaxis of influenza in adults and children five years of age and older	2006	Modified Indication	Small-molecule	Infectious Disease	N
Tacrolimus	Prograf	Prophylaxis of organ rejection in patients receiving allogeneic heart transplants	2006	New Indication	Small-molecule	Transplantation	Y
Cetuximab (1)	Erbitux	Use in combination with radiation therapy for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN)	2006	New Indication	Biologic	Oncology	N
Cetuximab (2)	Erbitux	Use as a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed	2006	New Indication	Biologic	Oncology	N
Fluvastatin	Lescol	Treatment of heterozygous familial hypercholesterolemia in adolescent boys and postmenarchal girls, ages 10 to 16 years	2006	Expanded patient population	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Ezetimibe	Zetia	Use in combination with fenofibrate, as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia	2006	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N

Daptomycin	Cubicin	Treatment of Staphylococcus aureus bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates	2006	New Indication	Small-molecule	Infectious Disease	N
Infliximab	Remicade	Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy	2006	Expanded patient population	Biologic	Gastroenterology	Y
Topotecan	Hycamtin	Use in combination with cisplatin for the treatment of Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy	2006	New Indication	Small-molecule	Oncology	N
Rivastigmine	Exelon	Treatment of mild to moderate dementia associated with Parkinson's Disease	2006	New Indication	Small-molecule	Neurology	N
Bimatoprost	Lumigan	Reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension [removes requirement of intolerance of other intraocular pressure lowering medications or insufficiently responsive to another intraocular pressure lowering medication]	2006	Modified Indication	Small-molecule	Ophthalmology	N
Aprepitant	Emend	Prevention of post-operative nausea and vomiting (PONV)	2006	New Indication	Small-molecule	Gastroenterology	N
Lenalidomide	Revlimid	Use in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy	2006	New Indication	Small-molecule	Oncology	Y
Bevacizumab	Avastin	Use as an adjunct to chemotherapy for the second-line treatment of patients with metastatic colorectal cancer	2006	Modified Indication	Biologic	Oncology	N
Natalizumab	Tysabri	Treatment of patients with relapsing forms of	2006	Modified	Biologic	Neurology	N

		multiple sclerosis (MS) to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations		Indication			
Famciclovir	Famvir	Treatment of recurrent herpes labialis (cold sores) in immunocompetent patients with a single dose of famciclovir 1500mg	2006	New Indication	Small-molecule	Infectious Disease	N
Gemcitabine	Gemzar	Use in combination with carboplatin for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy	2006	New Indication	Small-molecule	Oncology	N
Pegaspargase	Oncaspar	Use as a component of a multi-agent first-line chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL)	2006	Modified Indication	Biologic	Oncology	Y
Risedronate	Actonel	Treatment of osteoporosis in men	2006	Expanded patient population	Small-molecule	Musculoskeletal disease and rheumatology	N
Clopidogrel	Plavix	Reduce the rate of death from any cause and the rate of a combined endpoint of death, reinfarction or stroke for patients with ST-segment elevation acute myocardial infarction	2006	Modified Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Levetiracetam	Keppra	Use as adjunctive therapy of myoclonic seizures in adults and adolescents age 12 and over with juvenile myoclonic epilepsy	2006	New Indication	Small-molecule	Neurology	N
Ertapenem	Invanz	Prophylaxis of surgical site infection following elective colorectal surgery	2006	New Indication	Small-molecule	Infectious Disease	N
Infliximab (1)	Remicade	Inhibition of progression of structural damage of active psoriatic arthritis	2006	Modified Indication	Biologic	Musculoskeletal disease and rheumatology	Y
Infliximab (2)	Remicade	Improving physical function in patients with psoriatic arthritis	2006	Modified Indication	Biologic	Musculoskeletal disease and	Y

						rheumatology	
Lamotrigine	Lamictal	Adjunctive treatment of primary generalized tonic-clonic seizures in adults and pediatric patients	2006	New Indication	Small-molecule	Neurology	N
Imatinib mesylate	Gleevec	Use for newly diagnosed Philadelphia positive CML in pediatric patients	2006	Expanded patient population	Small-molecule	Oncology	Y
Rituximab	Rituxan	First-line treatment of follicular, CD20-positive, B-cell non-Hodgkin's lymphoma in combination with CVP chemotherapy	2006	New Indication	Biologic	Oncology	Y
Infliximab	Remicade	Treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate	2006	New Indication	Biologic	Musculoskeletal disease and rheumatology	Y
Risperidone	Risperdal	Treatment of the irritability associated with autistic disorder	2006	New Indication	Small-molecule	Psychiatry	N
Docetaxel	Taxotere	Use in combination with cisplatin and fluorouracil for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN)	2006	New Indication	Small-molecule	Oncology	N
Quetiapine fumarate	Seroquel	Treatment of major depressive episodes associated with bipolar disorder	2006	Modified Indication	Small-molecule	Psychiatry	N
Donepezil	Aricept	Treatment of dementia of the Alzheimer's type in patients with severe Alzheimer's Disease	2006	Modified Indication	Small-molecule	Neurology	N
Imatinib mesylate (1)	Gleevec	Treatment of adult dermafibrosarcoma protuberans (DFSP)	2006	New Indication	Small-molecule	Oncology	Y
Imatinib mesylate (2)	Gleevec	Treatment of adult myelodysplastic syndrome/myeloproliferative diseases (MDS/MPD)	2006	New Indication	Small-molecule	Oncology	Y

Imatinib mesylate (3)	Gleevec	Treatment of adult Ph+ acute lymphoblastic leukemia (ALL) as monotherapy	2006	New Indication	Small-molecule	Oncology	Y
Imatinib mesylate (4)	Gleevec	Treatment of adult aggressive systemic mastocytosis (ASM)	2006	New Indication	Small-molecule	Oncology	Y
Imatinib mesylate (5)	Gleevec	Treatment of adult hypereosinophilic syndrome/chronic eosinophilic leukemia (HES/CEL)	2006	New Indication	Small-molecule	Oncology	Y
Infliximab	Remicade	Maintenance of clinical remission and mucosal healing in the treatment of patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response to conventional therapy	2006	Modified Indication	Biologic	Gastroenterology	Y
Bevacizumab	Avastin	First-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer, in combination with carboplatin and paclitaxel	2006	New Indication	Biologic	Oncology	N
Pramipexole	Mirapex	Treatment of moderate-to-severe primary Restless Legs Syndrome (RLS)	2006	New Indication	Small-molecule	Neurology	N
Trastuzumab	Herceptin	Use as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel, for the adjuvant treatment of patients with HER2-overexpressing, node-positive breast cancer	2006	Modified Indication	Biologic	Oncology	N
Adalimumab	Humira	Inhibition of the progression of structural damage and improving physical function in patients with psoriatic arthritis	2006	Modified Indication	Biologic	Musculoskeletal disease and rheumatology	Y
Bortezomib	Velcade	Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy	2006	New Indication	Small-molecule	Oncology	Y
Exenatide synthetic	Byetta	Use in patients with type 2 diabetes mellitus who are using a thiazolidinedione alone or in combination with metformin but have not achieved adequate glycemic control	2006	Modified Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N

Balsalazide disodium	Colazal	Treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older	2006	Expanded patient population	Small-molecule	Gastroenterology	N
Celecoxib	Celebrex	Relief of the signs and symptoms of juvenile rheumatoid arthritis (JRA) in patients 2 years of age and older	2006	New Indication	Small-molecule	Musculoskeletal disease and rheumatology	N
Cardesartan cilexetil	Atacand	Treatment of heart failure (NYHA class II-IV and ejection fraction ≤40%) to reduce the risk of death from cardiovascular causes and to reduce hospitalizations for heart failure	2005	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Rosiglitazone	Avandia	Use in combination with a sulfonylurea and metformin to treat patients with type 2 diabetes mellitus	2005	Modified Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Peginterferon alfa-2a	Pegasys	Use alone or in combination with ribavirin USP (Copegus) for treatment of adult chronic hepatitis C patients coinfected with HIV, who have clinically stable HIV disease	2005	Modified Indication	Biologic	Infectious Disease	N
Temozolomide	Temodar	Treatment of patients with newly diagnosed high grade gliomas concomitantly with radiotherapy and then as adjuvant treatment	2005	New Indication	Small-molecule	Oncology	Y
Aripiprazole	Abilify	Maintenance therapy in Bipolar I Disorder	2005	Modified Indication	Small-molecule	Psychiatry	N
Bortezomib	Velcade	Treatment of multiple myeloma patients who have received at least one prior therapy [previous indication was for treatment of multiple myeloma patients who received at least 2 prior therapies]	2005	Modified Indication	Small-molecule	Oncology	Y
Ropinirole	Requip	Treatment of moderate-to-severe primary Restless Legs Syndrome (RLS)	2005	New Indication	Small-molecule	Neurology	N

Cardesartan cilexetil	Atacand	Added effect when used with an ACE inhibitor on the treatment of heart failure (NYHA class II-IV and ejection fraction ≤40%) to reduce the risk of death from cardiovascular causes and to reduce hospitalizations for heart failure	2005	Modified Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Ertapenem	Invanz	Use to treat multiple types of infections in the pediatric population	2005	Expanded patient population	Small-molecule	Infectious Disease	N
Fondaparinux	Arixtra	Use in patients undergoing abdominal surgery who are at risk for thromboembolic complications	2005	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Meropenem	Merrem	Treatment for patients with complicated skin and skin structure infections (cSSSI)	2005	New Indication	Small-molecule	Infectious Disease	N
Infliximab	Remicade	Treatment of psoriatic arthritis	2005	New Indication	Biologic	Musculoskeletal disease and rheumatology	Y
Peginterferon alfa-2a	Pegasys	Treatment of adult patients with HBe Antigen positive and HBe Antigen negative chronic hepatitis B who have compensated liver disease and evidence of viral replication and liver inflammation	2005	New Indication	Biologic	Infectious Disease	N
Topiramate	Topamax	Use as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures	2005	Modified Indication	Small-molecule	Neurology	N
Bivalirudin	Angiomax	Use with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI)	2005	New Indication	Small-molecule	Cardiovascular disease, diabetes, dyslipidemia	N
Capecitabine	Xeloda	Use as adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred	2005	Modified Indication	Small-molecule	Oncology	N

Moxifloxacin	Avelox	Treatment of adults with complicated skin and skin structure infections	2005	Modified Indication	Small-molecule	Infectious Disease	N
Levetiracetam	Keppra	Use as adjunctive therapy in the treatment of partial onset seizures in children 4 years of age and older with epilepsy	2005	Expanded patient population	Small-molecule	Neurology	N
Nitazoxanide	Alinia	Treatment of diarrhea caused by Crytosporidium parvum in non-HIV infected patients 12 years of age and older	2005	Expanded patient population	Small-molecule	Infectious Disease	Y
Montelukast	Singulair	Relief of symptoms of perennial allergic rhinitis (PAR) in adults and pediatric patients 6 months of age and older	2005	Modified Indication	Small-molecule	Allergy and Pulmonology	N
Celecoxib	Celebrex	Relief of signs and symptoms of ankylosing spondylitis	2005	New Indication	Small-molecule	Musculoskeletal disease and rheumatology	N
Exemestane	Aromasin	Adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy	2005	New Indication	Small-molecule	Oncology	Y
Ertapenem	Invanz	Treatment of adult diabetic foot infections without osteomyelitis	2005	Modified Indication	Small-molecule	Infectious Disease	N
Aprepitant	Emend	Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy	2005	Modified Indication	Small-molecule	Gastroenterology	N
Ritonavir	Norvir	Use in combination with other antiretroviral agents for the treatment of HIV-infection in pediatric patients from one month to two years of age	2005	Expanded patient population	Small-molecule	Infectious Disease	N
Oxcarbazepine	Trileptal	Use as adjunctive therapy in the treatment of partial seizures in children with epilepsy aged	2005	Expanded patient	Small-molecule	Neurology	N

		two to four years		population			
Adalimumab (1)	Humira	Treatment of psoriatic arthritis	2005	New Indication	Biologic	Musculoskeletal disease and rheumatology	Y
Adalimumab (2)	Humira	Treatment of recently diagnosed patients with moderately to severely active rheumatoid arthritis who have not received methotrexate	2005	Modified Indication	Biologic	Musculoskeletal disease and rheumatology	Y
Bivalirudin	Angiomax	Use for patients with, or at risk of, HIT/HITTS undergoing PCI	2005	New Indication	Small-molecule	Hematology	N
Moxifloxacin	Avelox	Treatment of complicated intra-abdominal infections	2005	New Indication	Small-molecule	Infectious Disease	N
Sodium oxybate	Xyrem	Treatment of excessive daytime sleepiness in patients with narcolepsy	2005	Modified Indication	Small-molecule	Neurology	Y
Erlotinib	Tarceva	Use in combination with gemcitabine for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer	2005	New Indication	Small-molecule	Oncology	N
Letrozole	Femara	Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer [removed requirement of having received 5 years of adjuvant tamoxifen therapy]	2005	Modified Indication	Small-molecule	Oncology	N
Oseltamivir	Tamiflu	Prophylaxis of influenza for patients between 1-12 years of age	2005	Expanded patient population	Small-molecule	Infectious Disease	N

*Generic drug names followed by numbers in parentheses denotes multiple supplemental indications which were concurrently approved by the FDA