Table S1: Anatomical Therapeutic Chemical (ATC) Classification and originally approved indication for new therapeutic biologics

Proprietary Name	Established Name	Indication(s)
Alimentary Tract and Metabolism ATC Classification		
Fabrazyme	Agalsidase beta	Indicated for use in patients with Fabry disease. Reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types.
Aldurazyme	Laronidase	Indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms.
Naglazyme	Galsulfase	Indicated for patients with Mucopolysaccharidosis VI (MPS VI).
Myozyme	Alglucosidase alfa	Indicated for patients with Pompe disease (GAA deficiency).
Elaprase	Idursulfase	Indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).
Lumizyme	Alglucosidase alfa (2000L)	Indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy.
Myalept	Metreleptin	Indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.
Tanzeum	Albiglutide	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Vimizim	Elosulfase alfa	Indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).
Trulicity	Dulaglutide	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Antiinfectives for Systemic use ATC Classification		
Raxibacumab	Raxibacumab	Indicated for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.
Antineoplastic and Immunomodulating Agents ATC Classification		
Pegasys	Peginterferon alfa-2a	Indicated for the treatment of adults with chronic hepatitis C who have compensated liver disease and who have not been previously treated with interferon alfa, including patients with compensated cirrhosis.
Amevive	Alefacept	Indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.
Humira	Adalimumab	Indicated for reducing signs and symptoms and inhibiting 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 disease-modifying anti-rheumatic drugs (DMARDs).
Raptiva	Efalizumab	Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Erbitux	Cetuximab	Used in combination with irinotecan, it is indicated for the treatment of epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Administered as a single agent, it is indicated for the treatment of EGFR expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.
Avastin	Bevacizumab	Used in combination with intravenous 5-fluorouracil–based chemotherapy, is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.
Tysabri	Natalizumab	Indicated in the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations.
Orencia	Abatacept	Indicated for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had and

		inadequate response to one or more DMARDs, such as methotrexate or TNF antagonists. Abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.
Vectibix	Panitumumab	Indicated for the treatment of EGFR-expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan- containing chemotherapy regimens.
Cimzia	Certolizumab pegol	Indicated for reducing signs and symptoms of Crohn' s disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
Soliris	Eculizumab	Indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.
Arcalyst	Rilonacept	Indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.
Stelara	Ustekinumab	Indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
Actemra	Tocilizumab	Indicated for treatment of adult patients with moderately-to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies
Nulojix	Belatacept	Indicated for prophylaxis of organ rejection in adult patients receiving kidney transplant. NULOJIX is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.
Simponi	Golimumab	Indicated for the treatment of moderately to severely active rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis in adults, alone or in combination with methotrexate.
Granix	tbo-filgrastim	Indicated for the reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Ilaris	Canakinumab	Indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).
Arzerra	Ofatumumab	Indicated for the treatment of chronic lymphocytic leukemia (CLL) refractory to alemtuzumab and fludarabine.
Erwinaze	Erwinia L-asparaginase	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to *E. coli*-derived asparaginase.
Benlysta	Belimumab	Indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.
Yervoy	Ipilimumab	Indicated for the treatment of unresectable or metastatic melanoma.
Adcetris	Brentuximab vedotin	Indicated for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen.
Perjeta	Pertuzumab	Indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
Zaltrap	Ziv-aflibercept	In combination with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.
Kadcyla	ado-Trastuzumab emtansine	Indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination.
Entyvio	Vedolizumab	Indicated for adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids; also indicated for adult patients with moderately to severely active Crohn's Disease who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.
Cyramza	Ramucirumab	Indicated for the treatment of advanced gastric cancer or gastro-esophageal junction adenocarcinoma, as a single-agent after prior fluoropyrimidine-or platinum-containing therapy.

Gazyva	Obinutuzumab	In combination with chlorambucil, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia.
Sylvant	Siltuximab	Indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.
Plegridy	Peginterferon beta-1a	Indicated for the treatment of patients with relapsing forms of multiple sclerosis.
Keytruda	Pembrolizumab	Indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
Opdivo	Nivolumab	Indicated for the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
Blincyto	Blinatumomab	Indicated for treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).
Blood and Blood Forming Organs ATC Classification		
Mircera	Pegzerepoetin alfa	Indicated for the treatment of anemia associated with chronic renal failure in adults, including patients on or not on dialysis.
Nplate	Romiplostim	Indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
Kalbitor	Ecallantide	Indicated for the treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older.
Musculo-skeletal system ATC Classification		
Dysport	Abobotulinumtoxin A	Indicated for the treatment of adults with cervical dystonia and for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients < 65 years of age.
Krystexxa	Pegloticase	Indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.
Prolia	Denosumab	Indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture.
Xiaflex	Clostridial collagenase	Indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord.
Xeomin	Incobotulinumtoxin A	Indicated for the treatment of adults with cervical dystonia, to decrease the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients; and in the treatment of blepharospasm in adults previously treated with onabotulium toxin A.
Respiratory System ATC Classification		
Xolair	Omalizumab	Indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.
Sensory Organs ATC Classification		
Lucentis	Ranibizumab	Indicated for the treatment of patients with neovascular (wet) age-related macular degeneration.
Eylea	Aflibercept	Indicated for treatment of neovascular (wet) age-related macular degeneration
Jetrea	Ocriplasmin	Indicated for the treatment of symptomatic vitreomacular adhesion.
Various ATC Classification		
NeutroSpec	Technetium (99m Tc) fanolesomab	Indicated for scintigraphic imaging of patients with equivocal signs and symptoms of appendicitis who are five years of age or older.
Bexxar	Tositumomab and Iodine I 131 Tositumomab	Indicated for the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy.
Kepivance	Palifermin	Indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.
Voraxaze	Glucarpidase	Indicated for the treatment of toxic (> 1 micromole per liter) plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function.

Table S2: Number of label updates and safety issues added to each section of the label for new therapeutic biologics (NTB)

Safety-related Section	NTB (n=61)		
	Number of products with any update[a]	Number of Label Updates[a]	Number of Safety Issues[a]
Any of the 5 sections of the label	54	214	1102
Boxed Warning	20	27	94
Warnings and Precautions	45	135	424
Contraindications	21	25	47
Adverse Reactions	47	142	652
Drug Interactions	7	8	14

[a]A single label update could be associated with one or more new safety issues, and a single safety issue could result in an update to one or more sections of the label.

Table S3: Number of label updates and number of issues for new therapeutic biologics (NTB) and new molecular entity (NME) by section of the label

A. Number of Label Updates – Whole study period

Safety-related Section	NTB (n=61) Number of Label Updates					NME (n=278) Number of Label Updates					
	Number of products with any update	Number of Label Updates	Mean ± SD	Median[a] (Min, Max)	IQR	Number of products with any update	Number of Label Updates	Mean ± SD	Median[a] (Min, Max)	IQR	Wilcoxon P - Value
Any of the 5 sections of the label	54	214	3.5±3.2	3 (0, 17)	(1, 5)	221	891	3.2±3.3	2 (0, 18)	(1, 5)	0.28
Boxed Warning	20	27	0.4±0.7	0 (0, 3)	(0, 1)	35	40	0.1±0.4	0 (0, 3)	(0, 0)	<0.001
Warnings and Precautions	45	135	2.2±2.5	2 (0, 12)	(0, 3)	176	452	1.6±1.9	1 (0, 9)	(0, 2)	0.07
Contraindications	21	25	0.4±0.6	0 (0, 2)	(0, 1)	75	106	0.4±0.8	0 (0, 5)	(0, 1)	0.30
Adverse Reactions	47	142	2.3±2.1	2 (0, 9)	(1, 3)	194	558	2.0±2.3	1 (0, 11)	(0, 3)	0.08
Drug Interactions	7	8	0.1±0.4	0 (0, 2)	(0, 0)	73	113	0.4±0.9	0 (0, 8)	(0, 1)	0.01

B. Number of Safety Issues – Whole study period

Safety-related Section	NTB (n=61) Number of Safety Issues					NME (n=278) Number of Safety Issues					
	Number of products with any update	Number of Safety Issues	Mean ± SD	Median[a] (Min, Max)	IQR	Number of products with any update	Number of Safety Issues	Mean ± SD	Median[a] (Min, Max)	IQR	Wilcoxon P - Value
Any of the 5 sections of the label	54	1102	18.1±19.7	10 (0, 91)	(4, 25)	221	2955	10.6±12.3	7 (0, 59)	(1, 15)	0.008
Boxed Warning	20	94	1.5±3.5	0 (0, 18)	(0, 1)	35	76	0.3±1.0	0 (0, 9)	(0, 0)	<0.001
Warnings and Precautions	45	424	7.0±8.1	3 (0, 28)	(0, 13)	176	1073	3.9±5.4	2 (0, 34)	(0, 5)	0.01
Contraindications	21	47	0.8±1.5	0 (0, 6)	(0, 1)	75	169	0.6±1.6	0 (0, 12)	(0, 1)	0.23
Adverse Reactions	47	652	10.7±13.8	5 (0, 75)	(1, 15)	194	1816	6.5±8.8	3 (0, 51)	(0, 9)	0.02
Drug Interactions	7	14	0.2±0.9	0 (0, 6)	(0, 0)	73	164	0.6±1.4	0 (0, 9)	(0, 1)	0.01

C. Number of Label Updates – 3.5 years of follow-up

Safety-related Section	NTB (n=61) Number of Label Updates					NME (n=278) Number of Label Updates					
	Number of products with any update	Number of Label Updates	Mean ± SD	Median[a] (Min, Max)	IQR	Number of products with any update	Number of Label Updates	Mean ± SD	Median[a] (Min, Max)	IQR	Wilcoxon P - Value
Any of the 5 sections of the label	43	90	1.5 ±1.6	1 (0, 8)	(0, 2)	172	345	1.2±1.4	1 (0, 8)	(0, 2)	0.27
Boxed Warning	12	14	0.2±0.5	0 (0, 2)	(0, 0)	21	22	0.1±0.3	0 (0, 2)	(0, 0)	0.004
Warnings and Precautions	35	67	1.1±1.5	1 (0, 8)	(0, 1)	118	184	0.7±0.9	0 (0, 5)	(0, 1)	0.02
Contraindications	13	16	0.3±0.5	0 (0, 2)	(0, 0)	40	46	0.2±0.4	0 (0, 3)	(0, 0)	0.16
Adverse Reactions	36	56	0.9±1.0	1 (0, 4)	(0, 1)	123	201	0.7±1.1	0 (0, 6)	(0, 1)	0.06
Drug Interactions	12	6	0.1±0.4	0 (0, 2)	(0, 0)	37	46	0.2±0.5	0 (0, 4)	(0, 0)	0.28

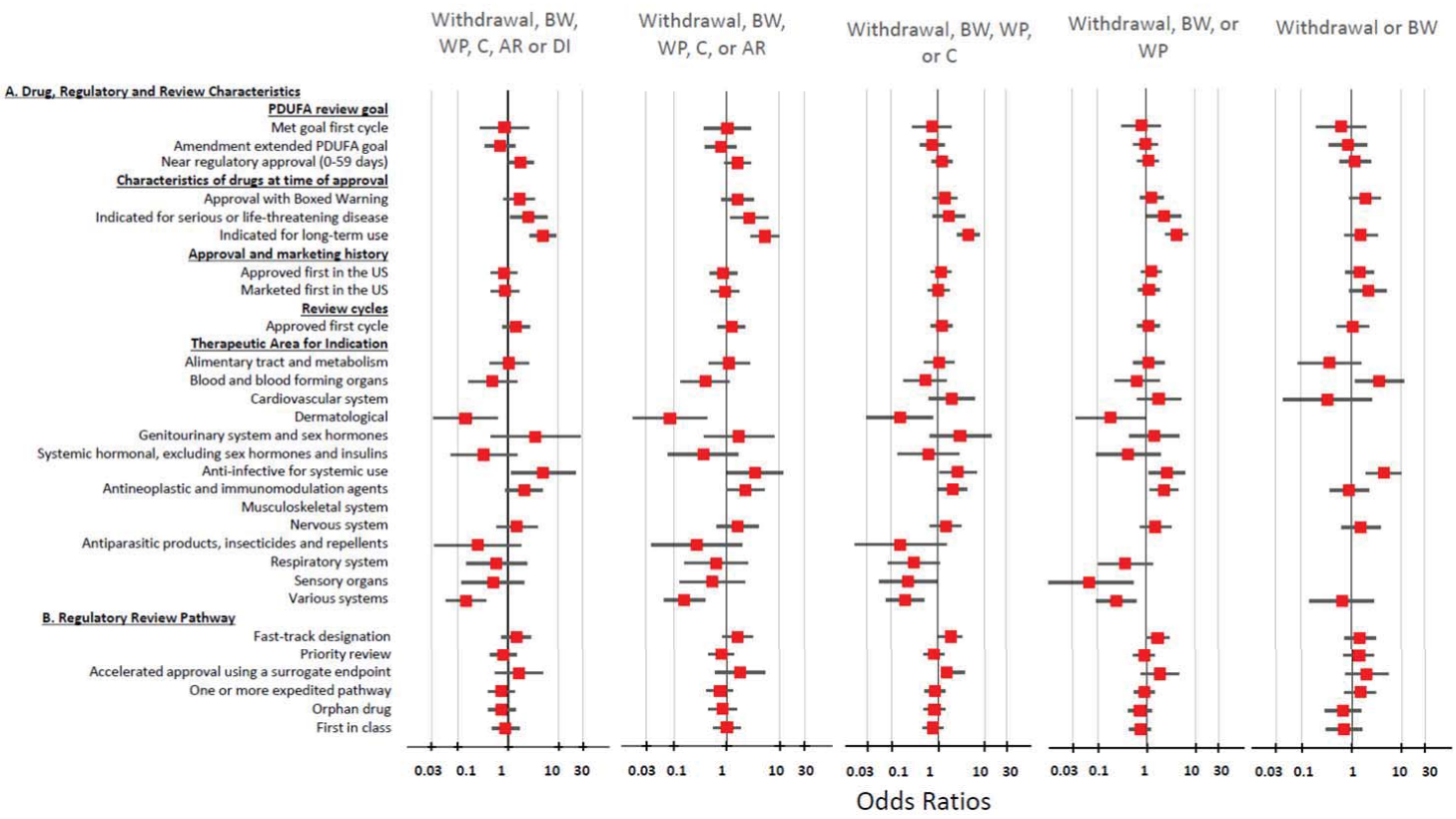
D. Number of Safety Issues – 3.5 years of follow-up

Safety-related Section	NTB (n=61) Number of Safety Issues					NME (n=278) Number of Safety Issues					
	Number of products with any update	Number of Safety Issues	Mean ± SD	Median[a] (Min, Max)	IQR	Number of products with any update	Number of Safety Issues	Mean ± SD	Median[a] (Min, Max)	IQR	Wilcoxon P - Value
Any of the 5 sections of the label	43	532	8.7±13.0	3 (0, 51)	(0, 12)	172	1212	4.4±6.7	1 (0, 46)	(0, 6)	0.04
Boxed Warning	12	35	0.6±1.8	0 (0, 11)	(0, 0)	21	39	0.1 ±0.7	0 (0, 8)	(0, 0)	0.003
Warnings and Precautions	35	216	3.5±5.1	1 (0, 19)	(0, 5)	118	425	1.5±3.0	0 (0, 23)	(0, 2)	0.003
Contraindications	13	24	0.4±1.0	0 (0, 5)	(0, 0)	40	71	0.3±0.9	0 (0, 8)	(0, 0)	0.17
Adverse Reactions	36	318	5.2±9.3	1 (0, 45)	(0, 7)	123	758	2.7±5.3	0 (0, 35)	(0, 3)	0.02
Drug Interactions	12	12	0.2±0.9	0 (0, 6)	(0, 0)	37	67	0.2±0.8	0 (0, 8)	(0, 0)	0.28

[a] The median value of zero reflects that fact that in any given year most products were not the subject of a safety-related label update in the specified section of the label.
IQR = interquartile range

Table S4: Number and percent of new therapeutic biologics (NTB) and new molecular entity (NME) drugs with a postmarketing safety update by section of the label update and Anatomical Therapeutic Chemical (ATC) Classification System

	Postmarketing update to *Boxed Warning* section of the label		Postmarketing update to *Warnings and Precautions* section of the label		Postmarketing update to *Contraindications* section of the label		Postmarketing update to *Adverse Reactions* section of the label		Postmarketing update to *Drug Interactions* section of the label	
ATC Classification	NTBs (n/N, %)	NMEs (n/N, %)	NTBs (n/N, %)	NMEs (n/N, %)	NTBs (n/N, %)	NMEs (n/N, %)	NTBs (n/N, %)	NMEs (n/N, %)	NTBs (n/N, %)	NMEs (n/N, %)
Alimentary tract and metabolism	4/10 (40.0%)	2/35 (5.7%)	9/10 (90.0%)	23/35 (65.7%)	3/10 (6.7%)	7/35 (20.0%)	8/10 (80.0%)	25/35 (71.4%)	0/10 (0%)	5/35 (14.3%)
Blood and blood forming organs	1/3 (33.3%)	4/15 (26.7%)	2/3 (66.7%)	8/15 (53.3%)	1/3 (33.3%)	5/15 (33.3%)	2/3 (66.7%)	7/15 (46.7%)	0/3 (0%)	3/15 (20.0%)
Cardiovascular system	0/0	1/20 (5.0%)	0/0	15/20 (75.0%)	0/0	8/20 (40.0%)	0/0	17/20 (85.0%)	0/0	8/20 (40.0%)
Dermatological	0/0	0/8 (0%)	0/0	2/8 (25.0%)	0/0	1/8 (12.5%)	0/0	2/8 (25.0%)	0/0	1/8 (12.5%)
Genitourinary system and sex hormones	0/0	0/14 (0%)	0/0	10/14 (71.4%)	0/0	6/14 (42.9%)	0/0	10/14 (71.4%)	0/0	3/14 (21.4%)
Systemic hormonal preparations, excluding sex hormones and insulins	0/0	0/7 (0%)	0/0	3/7 (42.9%)	0/0	2/7(28.6%)	0/0	4/7 (57.1%)	0/0	0/7 (0%)
Antiinfective agents for systemic use	0/1 (0%)	12/36 (33.3%)	0/1 (0%)	29/36 (80.6%)	0/1 (0%)	14/36 (38.9%)	0/1 (0%)	30/36 (83.3%)	0/1 (0%)	19/36 (52.8%)
Antineoplastic and immunomodulation agents	13/34 (38.2%)	7/57 (12.3%)	28/34 (82.4%)	44/57 (77.2%)	13/34 (38.2%)	8/57 (14.0%)	27/34 (79.4%)	46/57 (80.7%)	7/34 (20.6%)	14/57 (24.6%)
Musculoskeletal system	1/5 (20.0%)	0/2 (0%)	4/5 (80.0%)	2/2 (100%)	3/5 (60.0%)	1/2 (50.0%)	3/5 (60.0%)	2/2 (100%)	0/5 (0%)	1/2 (50.0%)
Nervous system	0/0	7/39 (18.0%)	0/0	28/39 (71.8%)	0/0	13/39 (33.3%)	0/0	29/39 (74.4%)	0/0	14/39 (35.9%)
Antiparasitic products, insecticides and repellents	0/0	0/4 (0%)	0/0	0/4 (0%)	0/0	1/4 (25.0%)	0/0	2/4 (50.0%)	0/0	2/4 (50.0%)
Respiratory system	1/1 (100%)	0/10 (0%)	1/1 (100%)	4/10 (40.0%)	0/1 (0%)	2/10 (20.0%)	1/1 (100%)	6/10 (60.0%)	0/1 (0%)	0/10 (0%)
Sensory organs	0/3 (0%)	0/9 (0%)	0/3 (0%)	1/9 (11.1%)	1/3 (33.3%)	3/9 (33.3%)	3/3 (100%)	6/9 (66.7%)	0/3 (0%)	0/9 (0%)
Various systems	0/4 (0%)	2/22 (9.1%)	1/4 (25.0%)	7/22 (31.8%)	0/4 (0%)	4/22 (18.2%)	3/4 (75.0%)	8/22 (36.4%)	0/4 (0%)	3/22 (13.6%)
Total	20/61 (32.8%)	35/278 (12.6%)	45/61 (73.8%)	176/278 (63.1%)	21/61 (34.4%)	75/278 (27.0%)	47/61 (77.1%)	194/278 (69.8%)	7/61 (11.5%)	73/278 (26.3%)



BW, *Boxed Warning*; WP, *Warnings and Precautions*; C, *Contraindications*; AR, *Adverse Reactions*; DI, *Drug Interactions*. N=277, excludes one NME that was approved but never marketed; Forest plot not available for analyses where the independent covariate had a zero value in one of more of the formed 2 X 2 table cells.

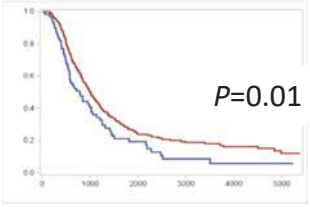
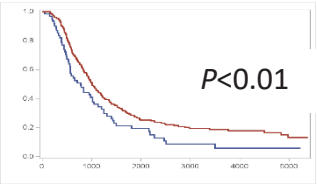
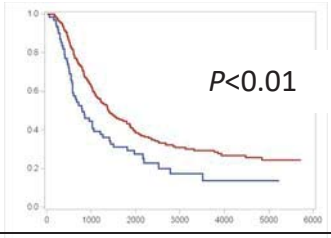
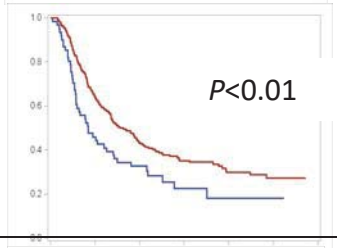
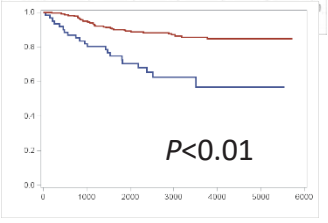
Figure S1: Relationship of regulatory, review characteristics, and safety-related regulatory actions for New Molecular Entities (n=278) approved by the FDA between October 1, 2002, and December 31, 2014.

Table S5: Logistic regression analysis for association between safety-related outcomes and therapeutic product type (new therapeutic biologics (NTB) vs. New Molecular Entity (NME) drugs). Variables were considered potential confounders if they were associated with the safety-related regulatory action at $P<0.10$, or if they had been considered to be important confounders of the occurrence of any safety-related regulatory actions or serious safety-related regulatory actions in the published literature. A backwards, stepwise logistic regression analysis was performed to determine the independent predictors of the dichotomous outcome. Potential confounders that had a P-value of <0.05 were included in the multivariable models.

NTB vs. NME	**Safety-related regulatory action**				
	Withdrawal, BW, WP, C, AR or DI	Withdrawal, BW, WP, C or AR	Withdrawal, BW, WP or C	Withdrawal, BW or WP	Withdrawal or BW
Unadjusted Odds Ratio (95% CI)	2.36 (0.97-5.77); *P*=0.059	2.58 (1.06-6.27); *P*=0.04	1.99 (1.01-3.92); *P*=0.048	1.78 (0.94-3.34); *P*=0.08	3.53 (1.87-6.65); *P*<0.01
Adjusted Odds Ratio (95% CI)	2.39 (0.94-6.07); *P*=0.07[a]	2.66 (1.04-6.80); *P*=0.04[a]	1.97 (0.96-4.05); *P*=0.07[a]	1.43 (0.71-2.89); *P*=0.32[b]	3.09 (1.58-6.04); *P*=0.001[c]

[a] Adjusted for length of follow-up, and indication for long-term use
[b] Adjusted for length of follow-up and indication for long-term use, and antineoplastic and immunomodulation agent ATC
[c] Adjusted for length of follow-up, and approval with a *Boxed Warning* section

BW, *Boxed Warning*; WP, *Warnings and Precautions*; C, *Contraindications*; AR, *Adverse Reactions*; DI, *Drug Interactions*.

	Kaplan Meier curves	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Withdrawal, BW, WP, C, AR or DI		**1.40 (1.04-1.89); *P*=0.02**	**1.26 (0.93-1. 71)[a]; *P*=0.14**
Withdrawal, BW, WP, C or AR		**1.46 (1.09-1.97); *P*=0.01**	**1.31 (0.98-1.77)[b]; *P*=0.07**
Withdrawal, BW, WP or C		**1.59 (1.16-2.17); *P*<0.01**	**1.32 (0.95-1.82)[c]; *P*=0.10**
Withdrawal, BW or WP		**1.55 (1.12-2.14); *P*<0.01**	**1.33 (0.96-1.86)[d]; *P*=0.10**
Withdrawal or BW		**3.31 (1.03-5.68); *P*<0.001**	**2.85 (1.64-4.93)[e]; *P*<0.001**
	NTB NME		

[a] Adjusted for indication for long-term use, orphan designation, approval using a surrogate endpoint, and antineoplastic and immunomodulation agent ATC
[b] Adjusted for indication for long-term use, and accelerated approval using a surrogate endpoint
[c] Adjusted for indication for long-term use, and antineoplastic and immunomodulation agent ATC
[d] Adjusted for indication for long-term use, accelerated approval using a surrogate endpoint, and antineoplastic and immunomodulation agent ATC
[e] Adjusted for approved with a *Boxed Warning*, and accelerated approval using a surrogate endpoint

BW, *Boxed Warning*; WP, *Warnings and Precautions*; C, *Contraindications*; AR, *Adverse Reactions*; DI, *Drug Interactions*.

Figure S2: Time to first safety-related regulatory action comparing new therapeutic biologics (NTB) and new molecular entities (NME) using Gehan-Breslow tests and Cox proportional hazards model hazard ratios comparing NTB vs. NME. Variables considered potential confounders if they were associated with the time to safety-related regulatory action at $P<0.10$ or if they had been considered to be important confounders of safety-related regulatory actions in the published literature. Evaluation of the proportional hazards assumptions testing was done by evaluating the graphic presentation of survival curves and through the ASSESS statement in SAS which examines the cumulative sums of martingale residuals over covariate values. Potential confounders that had a *P*-value of <0.05 were included in the multivariable models.

Table S6: Definitions of regulatory and review characteristics, regulatory review pathways, and safety-related regulatory actions

PDUFA[a] review goals	The Prescription Drug User Fee Act (PDUFA) was created by Congress in 1992. It authorizes FDA to collect fees from companies that produce certain human drug and biological products, and imposes FDA goals, generally 6 or 10 months, for FDA review of a new drug application. The timing for the review clock begins when the company submits or FDA files the new drug application to the FDA. The PDUFA goal date is a target decision date for FDA review cycles.
Met goal first cycle	FDA completed the first cycle review by the (PDUFA) goal date. This also takes into account changes to the goal date associated with the receipt of major amendments.
Amendment extended PDUFA goal	FDA extended the original first cycle goal date. The goal date may be extended by up to 3 months if a major amendment is submitted for review.
Near-regulatory approval (0-59 days)	Approval on or within the 59-day period before the first-cycle PDUFA goal date. For products that were not approved within the first-cycle PDUFA goal date, near-regulatory approval was classified as "no". For products which were approved within 59 days of the first-cycle PDUFA goal date, near-regulatory approval was classified as "yes"; otherwise near-regulatory approval was classified as "no".
Approved first cycle	Application was approved in one review cycle.
Indicated for serious[b] or life-threatening disease[c]	A serious disease or condition was defined as a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. A life-threatening disease was defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted, and diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival.
Indicated for long-term use	For the purposes of our analyses, long term use is defined as intended for chronic or repeated intermittent use for longer than 6 months.
Anatomical Therapeutic Chemical (ATC) classification [d]	The Anatomical Therapeutic Chemical (ATC) classification system groups therapeutic substances according to the organ or system on which they act, and according to their therapeutic, pharmacologic and chemical properties. It is controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC) and was first published in 1976.
Regulatory review pathway	**Definition**

Fast-track designation[b]	Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need, or designated as a qualified infectious disease product. For the purposes of our analyses, if two or more indications are approved at the same time with at least one indication designated as fast-track, the drug will be classified as fast-track.
Priority review[b]	Priority review status may be granted for an application for: (1) a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness; or (2) any supplement that proposes a labeling change pursuant to a report on a pediatric study; or (3) an application for a drug that has been designated as a qualified infectious disease product or any application or supplement for a drug submitted with a priority review voucher. There is a shorter clock for review of marketing applications under priority review. (6 months compared with 10 months with standard review). For the purposes of our analyses, if two or more indications are approved at the same time with at least one indication designated as priority review, the drug will be classified as priority review.
Accelerated approval using a surrogate endpoint[b]	An accelerated approval track may be granted for a drug that treats a serious condition and generally provides a meaningful advantage over available therapies. Accelerated approval is designed to shorten clinical development time to bring treatment for an unmet medical need quickly to market. For products granted accelerate approval a surrogate endpoint may be used in clinical trials as an indirect or substitute measurement that represents a clinically meaningful outcome, most of which are considered reasonably likely to predict a real clinical benefit. For the purposes of our analyses, if two or more indications are approved at the same time with at least one indication designated as accelerated approval using a surrogate endpoint, the drug will be classified as accelerated approval using a surrogate endpoint.
Breakthrough[b] designation	A breakthrough drug is one intended to treat a serious condition and one in which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies. The breakthrough designation was instituted on July 9, 2012 with the passage of Food and Drug Administration Safety and Innovation Act (FDASIA). For the purposes of our analyses, if two or more indications are approved at the same time with at least one indication designated as breakthrough the drug will be classified as a breakthrough designation.

Orphan designation[e]	An orphan designated product is a product intended to treat a rare disease that has received an orphan designation from the FDA prior to marketing approval. A rare disease is a disorder affecting less than 200,000 people in the United States. For the purposes of our analyses, if two or more indications are initially approved at the same time with at least one indication being a non-orphan indication, the drug will be classified as non-orphan to align with differences in premarket development program sizes of orphan and non-orphan products.
First-in-class[f]	First-in-class products are products that use a new and unique mechanism of action for treating a medical condition. First-in-class is an indicator of the innovative nature of a drug. A first-in-class product is the first therapeutic product approved within its respective product class. First-in-class products are pharmacologically innovative because each represents a new pathway for treating a disease. Although subsequent approvals within the same class may prove to have advantages over the first product, first-in-class products are genuinely innovative, because each represents a novel approach to drug therapy.
Safety-related regulatory action variable	**Definition**
Withdrawn or updates in 5 sections of the label	Withdrawal due to safety concerns or an update including an addition of a new safety issue to the: • *Boxed Warning* • *Warnings and Precautions* • *Contraindications* • *Adverse Reactions* • *Drug Interactions*
Withdrawn or updates in 4 sections of the label	Withdrawal due to safety concerns or an update including an addition of a new safety issue to the: • *Boxed Warning* • *Warnings and Precautions* • *Contraindications* • *Adverse Reactions*
Withdrawn or updates in 3 sections of the label	Withdrawal due to safety concerns or an update including an addition of a new safety issue to the: • *Boxed Warning* • *Warnings and Precautions* *Contraindications*

Withdrawn or updates in 2 sections of the label	Withdrawal due to safety concerns or an update including an addition of a new safety issue to the: • *Boxed Warning* • *Warnings and Precautions*
Withdrawn or updates in 1 section of the label	Withdrawal due to safety concerns or an update including an addition of a new safety issue to the: • *Boxed Warning*

Supplemental References:

a FDA. *Prescription Drug User Fee Amendment*, <https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments> (2020). Accessed 1 March 2020.

b FDA. *Guidance for Industry Expedited Programs for Serious Conditions — Drugs and Biologics* <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf> (2014). Accessed 1 March 2020.

c *Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses. Code of Federal Regulations Title 21, 312.81*., <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.81.> Accessed 1 March 2020.

d WHO. *ATC/DDD Index 2019*, <https://www.whocc.no/atc_ddd_index/> (2019). Accessed 1 March 2020.

e FDA. *Orphan Drug Designations and Approvals,* <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>. Accessed 1 March 2020.

f Lanthier, M. *et al*. An improved approach to measuring drug innovation finds steady rates of first-in-class pharmaceuticals, 1987-2011. *Health Aff. (Millwood)* **32**, 1433–1439 (2013).