SUPPLEMENTARY CONTENT

Postapproval Studies of Drugs Initially Approved by the FDA on the Basis of Limited Evidence: Systematic Review

Alison M. Pease, BS; Harlan M. Krumholz, MD, SM; Nicholas S. Downing, MD;

Jenerius A. Aminawung, MD, MPH; Nilay D. Shah, PhD; Joseph S. Ross, MD, MHS

TABLE OF CONTENTS

APPENDIX 1. Aggregated studies and patients enrolled among post-approval studies of novel therapeutics approved by the Food and Drug Administration between 2005 and 2012 on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease as primary endpoints, or both ("single/surrogate"), stratified by approval year category.

Appendix 1									
	Single Pivotal Approvals			Surrogate Marker Approvals			Single/Surrogate Marker Approvals		
	2005-2007 (n=11)	2008-2010 (n=10)	2011-2012 (n=12)	2005-2007 (n=19)	2008-2010 (n=16)	2011-2012 (n=15)	2005-2007 (n=14)	2008-2010 (n=11)	2011-2012 (n=16)
Median Trials Per Indication, No. (IQR)	0 (0-1)	1.5 (0-2.25)	0.5 (0-1)	5 (1-40)	2 (0-18)	3 (1-6)	3 (1-17.25)	1 (0-2)	0 (0-0)
p-value		0.36			0.17			< 0.0001	
Median Randomized/Double-Blind Trials, No. (IQR)	0 (0-0)	0 (0-2)	0 (0-1)	1 (0-9)	2 (0-3)	1 (0-3)	0 (0-1.5)	0 (0-1)	0 (0-0)
p-value		0.32			0.96			0.02	
Median Total Patients Enrolled, No. (IQR)	0 (0-233)	108 (0-1347)	162 (0-1036)	1207 (205-8130)	256 (0-2552)	1042 (100-2964)	796 (43-4423)	92 (0-471)	0 (0-0)
p-value		0.68			0.24			0.0003	
Median Intervention Patients Enrolled, No. (IQR)	0 (0-119)	67 (0-667)	110 (0-541)	696 (144-3821)	155 (0-1211)	641 (75-1733)	514 (21-2366)	63 (0-337)	0 (0-0)
p-value		0.67			0.23			0.0003	
Median Total Patient-Years Exposure, No. (IQR)	0 (0-135.0)	138.8 (0-558.8)	43.2 (0-677.5)	1210.3	101.2 (0-1513.6)	858.7 (76.6-2033.4)	1135.1	98.8 (0-790.8)	0 (0-0)

				(116.6-6594.9)			(15.4-4319.4)		
p-value		0.60			0.12			0.0005	
Median Intervention Patient-Years Exposure, No. (IQR)	0 (0-90.0)	49.4 (0-334.4)	18.0 (0-392.6)	661.1 (65.2-3729.0)	69.2 (0-741.3)	557.5 (39.2-832.2)	726.2 (8.1-2301.9)	61.2 (0-393.8)	0 (0-0)
p-value		0.61			0.13			0.0006	
Indications with ≥1 Trial, No. (%)	5 (45.5)	7 (70.0)	6 (50.0)	18 (94.7)	12 (75.0)	12 (80.0)	12 (85.7)	7 (63.6)	2 (12.5)
p-value		0.75			0.34			0.0001	
Indications with ≥1 Randomized/Double-Blind Trial, No. (%)	2 (18.2)	4 (40.0)	4 (33.3)	10 (52.6)	12 (75.0)	10 (66.7)	6 (42.9)	3 (27.3)	0 (0.0)
p-value		0.57			0.62			0.007	
Indications with ≥1 Randomized/Double-Blind Trial with a Clinical Primary Endpoint, No. (%)	2 (18.2)	4 (40.0)	4 (33.3)	1 (5.3)	2 (12.5)	1 (6.7)	3 (21.4)	0 (0.0)	0 (0.0)
p-value		0.57			0.82			0.16	
Indications with ≥1 Trial Demonstrating Superiority or	2 (18.2)	3 (30.0)	4 (33.3)	15 (78.9)	12 (75.0)	11 (73.3)	10 (71.4)	4 (36.4)	1 (6.3)

Non-Inferiority of the Primary Endpoint, No. (%)									
p-value		0.79			0.92			0.0008	
Indications with ≥1 Randomized/Double-Blind Trial Demonstrating Superiority or Non-Inferiority, No. (%)	1 (9.1)	2 (20.0)	4 (33.3)	10 (52.6)	11 (68.8)	8 (53.3)	4 (28.6)	2 (18.2)	0 (0.0)
p-value		0.44			0.82			0.06	
Indications with ≥1 Randomized/Double-Blind Trial Demonstrating Superiority or Non-Inferiority of a Clinical Primary Endpoint, No. (%)	1 (9.1)	2 (20.0)	3 (25.0)	0 (0.0)	1 (6.3)	1 (6.7)	2 (14.3)	0 (0.0)	0 (0.0)
p-value		0.74			0.52			0.35	

APPENDIX 2. Aggregated studies and patients enrolled among post-approval studies of novel therapeutics approved by the Food and Drug Administration between 2005 and 2012 on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease as primary endpoints, or both ("single/surrogate"), stratified by therapeutic area.

Appendix 2												
	Single Pivotal Approvals				Surrogate Marker Approvals				Single/Surrogate Marker Approvals			
	Cancer (n=9)	Cardio & DM (n=5)	ID (n=3)	Other (n=16)	Cancer (n=8)	Cardio & DM (n=13)	ID (n=11)	Other (n=18)	Cancer (n=24)	Cardio & DM (n=2)	ID (n=3)	Other (n=12)
Median Trials Per Indication, No. (IQR)*	1 (0-1.5)	3 (1-26.5)	0 (0-2)	0 (0-1)	1 (0-2.75)	18 (1.5-52)	6 (3-27)	2 (1-3.5)	0.5 (0-1.75)	23.5 (21-26)	1 (0-17)	0 (0-1)
p-value		0.08				0.003				0.07		
Median Randomized/ Double-Blind Trials, No. (IQR)*	0 (0-1)	1 (0-4)	0 (0-0)	0 (0-0.75)	0 (0-0)	5 (1-23.5)	1 (0-3)	1 (0-2)	0 (0-0)	2 (1-3)	0 (0-3)	0 (0-1)
p-value		0.24				0.0005				0.02		
Median Total Patients Enrolled, No. (IQR)	502 (0-1225)	1554 (258-10,141)	0 (0-389)	0 (0-122)	215 (0-708)	4332 (186.5-17,722)	2964 (1042-4955)	225 (122-603)	22 (0-712)	38,816 (4154-73,477)	440 (0-2164)	0 (0-60)

p-value		0.07				0.003				0.07		
Median Intervention Patients Enrolled, No. (IQR)	250 (0-632)	691 (55-3437)	0 (0-187)	0 (0-80)	121 (0-353)	3174 (94.5-9181)	863 (641-2472)	174 (104-466)	11 (0-381)	10,761 (2286-19,236)	218 (0-1098)	0 (0-57)
p-value		0.13				0.005				0.08		
Median Total Patient-Years Exposure, No. (IQR)	434.4 (0-1910.0)	233.0 (43.2-8978.8)	0 (0-68.6)	0 (0-168.2)	280.1 (0-1188.3)	2033.4 (70.8-8023.7)	3021.3 (961.8-5026.2)	101.2 (8.0-487.2)	39.8 (0-938.2)	20,387.8 (3379.7-37,396.0)	84.6 (0-1862.7)	0 (0-17.9)
p-value		0.24				0.004				0.09		
Median Intervention Patient-Years Exposure, No. (IQR)	216.3 (0-968.9)	42.0 (18.0-2058.1)	0 (0-32.7)	0 (0-91.2)	145.1 (0-622.9)	1131.7 (36.1-3966.6)	832.2 (591.7-2582.4)	69.2 (6.5-319.5)	19.0 (0-628.3)	5876.7 (1882.4-9871.1)	41.9 (0-915.3)	0 (0-13.3)
p-value		0.35				0.003				0.09		
Indications with ≥1 Trial	6 (66.7)	4 (80.0)	1 (33.3)	7 (43.8)	5 (62.5)	12 (92.3)	10 (90.9)	15 (83.3)	12 (50.0)	2 (100.0)	2 (66.7)	5 (41.7)
p-value		0.58				0.11				0.62		
Indications with ≥1 Randomized/	3 (33.3)	3 (60.0)	0 (0.0)	4 (25.0)	0 (0.0)	11 (84.6)	8 (72.7)	13 (72.2)	2 (8.3)	2 (100.0)	1 (33.3)	4 (33.3)

Double-Blind Trial												
p-value		0.36				0.0006				0.01		
Indications with ≥1 Randomized/ Double-Blind Trial with a Clinical Primary Endpoint	3 (33.3)	3 (60.0)	0 (0.0)	4 (25.0)	0 (0.0)	2 (15.4)	0 (0.0)	2 (11.1)	1 (4.2)	0 (0.0)	1 (33.3)	1 (8.3)
p-value		0.36				0.56				0.13		
Indications with ≥1 Trial Demonstrating Superiority or Non-Inferiority of the Primary Endpoint	3 (33.3)	3 (60.0)	1 (33.3)	2 (12.5)	3 (37.5)	11 (84.6)	10 (90.9)	14 (77.8)	7 (29.2)	2 (100.0)	2 (66.7)	4 (33.3)
p-value		0.14				0.07				0.15		
Indications with ≥1 Randomized/ Double-Blind	3 (33.3)	2 (40.0)	0 (0.0)	2 (12.5)	0 (0.0)	11 (84.6)	7 (63.6)	11 (61.1)	2 (8.3)	0 (0.0)	1 (33.3)	3 (25.0)

Trial Demonstrating Superiority or Non-Inferiority												
p-value		0.33				0.001				0.34		
Indications with ≥1 Randomized/ Double-Blind Trial Demonstrating Superiority or Non-Inferiority of a Clinical Primary Endpoint	2 (22.2)	2 (40.0)	0 (0.0)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	1 (4.2)	0 (0.0)	0 (0.0)	1 (8.3)
p-value		0.42				0.65				0.50		

APPENDIX 3. Aggregated studies and patients enrolled among post-approval studies of novel therapeutics approved by the Food and Drug Administration between 2005 and 2012 on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease as primary endpoints, or both ("single/surrogate"), stratified by expected length of treatment.

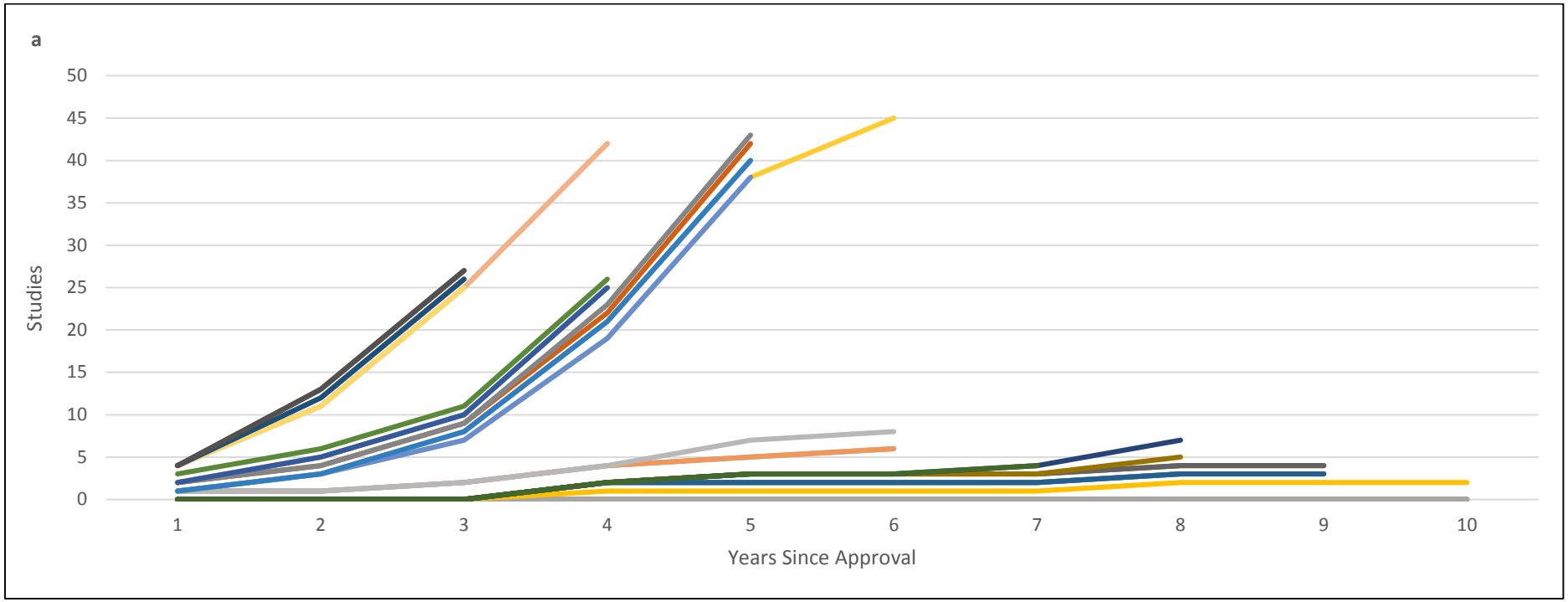
Appendix 3									
	Single Pivotal Approvals			Surrogate Marker Approvals			Single/Surrogate Marker Approvals		
	Acute (n=4)	Intermediate (n=12)	Chronic (n=17)	Acute (n=7)	Intermediate (n=9)	Chronic (n=34)	Acute (n=4)	Intermediate (n=24)	Chronic (n=13)
Median Trials Per Indication, No. (IQR)	0 (0-0.75)	1 (0.25-1.75)	0 (0-2)	1 (1-6)	1 (0-2.5)	4.5 (2-18.5)	1 (0.25-1)	0.5 (0-1.75)	0 (0-13.5)
p-value		0.49			0.02			0.86	
Median Randomized/Double-Blind Trials, No. (IQR)	0 (0-0.75)	0 (0-1)	0 (0-1)	1 (1-2)	0 (0-0)	1 (0-5.75)	0.5 (0-1)	0 (0-0)	0 (0-2)
p-value		0.93			0.005			0.06	
Median Total Patients Enrolled, No. (IQR)	0 (0-94)	173 (10-1036)	0 (0-453)	173 (100-455)	205 (0-605)	1381 (248-5749)	56 (12-346)	22 (0-712)	0 (0-3056)
p-value		0.48			0.03			0.98	
Median Intervention Patients Enrolled, No. (IQR)	0 (0-59)	100 (10-541)	0 (0-235)	143 (75-229)	138 (0-302)	777 (160-3336)	52 (10-179)	11 (0-381)	0 (0-1507)
p-value		0.43			0.03			0.98	
Median Total Patient-Years Exposure, No. (IQR)	0 (0-5.4)	195.8 (7.5-1592.7)	0 (0-251.7)	17.3 (2.1-830.3)	130.1 (0-941.7)	1064.9 (112.8-4218.8)	9.6 (1.2-67.1)	39.8 (0-938.2)	0 (0-2621.2)

p-value		0.30			0.02			0.96	
Median Intervention Patient-Years Exposure, No. (IQR)	0 (0-3.4)	98.8 (3.8-809.0)	0 (0-149.7)	10.3 (2.1-362.9)	69.0 (0-532.0)	614.7 (66.5-2353.3)	9.2 (1.0-35.1)	19.0 (0-628.3)	0 (0-1398.8)
p-value		0.25			0.02			0.98	
Indications with ≥1 Trial, No. (%)	1 (25.0)	9 (75.0)	8 (47.1)	6 (85.7)	5 (55.6)	30 (88.2)	3 (75.0)	12 (50.0)	6 (46.2)
p-value		0.63			0.13			0.73	
Indications with ≥1 Randomized/Double-Blind Trial, No. (%)	1 (25.0)	4 (33.3)	5 (29.4)	6 (85.7)	1 (11.1)	25 (73.5)	2 (50.0)	2 (8.3)	5 (38.5)
p-value		0.99			0.002			0.03	
Indications with ≥1 Randomized/Double-Blind Trial with a Clinical Primary Endpoint, No. (%)	1 (25.0)	4 (33.3)	5 (29.4)	1 (14.3)	0 (0.0)	3 (8.8)	0 (0.0)	1 (4.2)	2 (15.4)
p-value		0.99			0.56			0.13	
Indications with ≥1 Trial Demonstrating Superiority or Non-Inferiority of the Primary Endpoint, No. (%)	0 (0.0)	3 (25.0)	6 (35.3)	5 (71.4)	4 (44.4)	29 (85.3)	2 (50.0)	7 (29.2)	6 (46.2)
p-value		0.49			0.05			0.55	

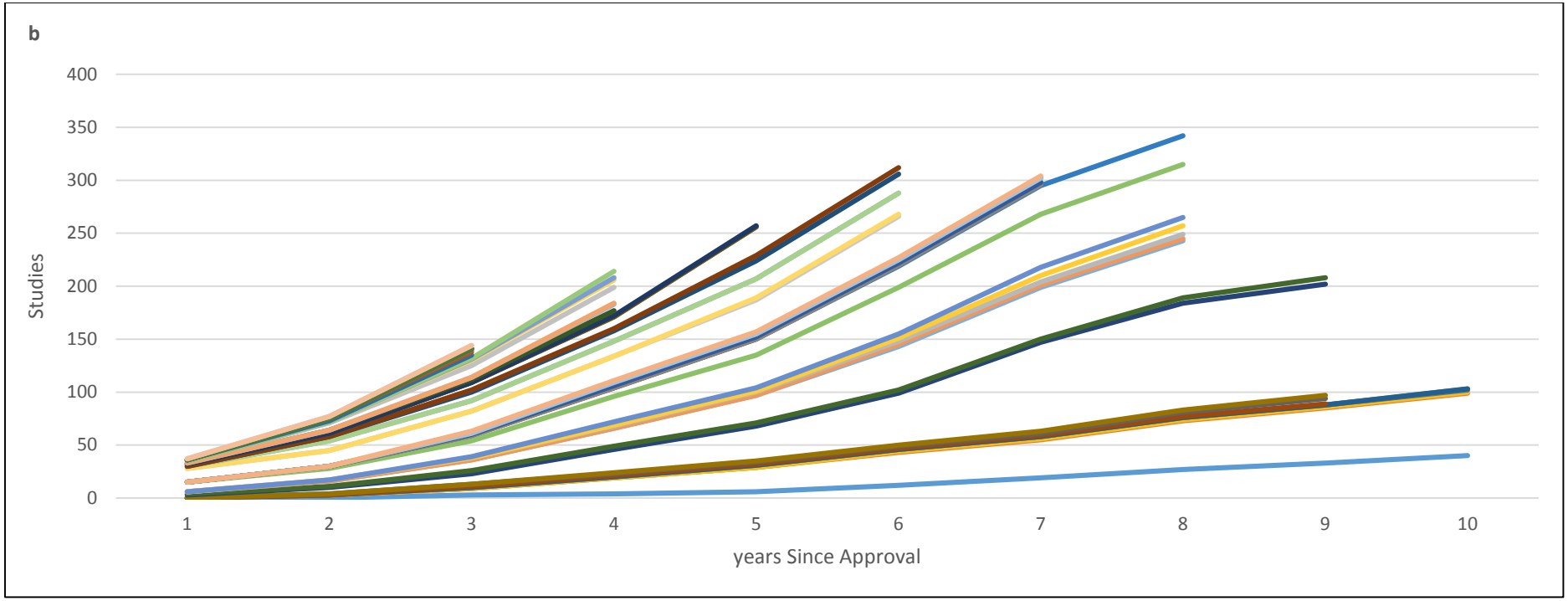
Indications with ≥1 Randomized/Double-Blind Trial Demonstrating Superiority or Non-Inferiority, No. (%)	0 (0.0)	3 (25.0)	4 (23.5)	5 (71.4)	1 (11.1)	23 (67.6)	1 (25.0)	2 (8.3)	3 (23.1)
p-value		0.71			0.01			0.30	
Indications with ≥1 Randomized/Double-Blind Trial Demonstrating Superiority or Non-Inferiority of a Clinical Primary Endpoint, No. (%)	0 (0.0)	2 (16.7)	4 (23.5)	1 (14.3)	0 (0.0)	1 (2.9)	0 (0.0)	1 (4.2)	1 (6.5)
p-value		0.84			0.29			0.47	

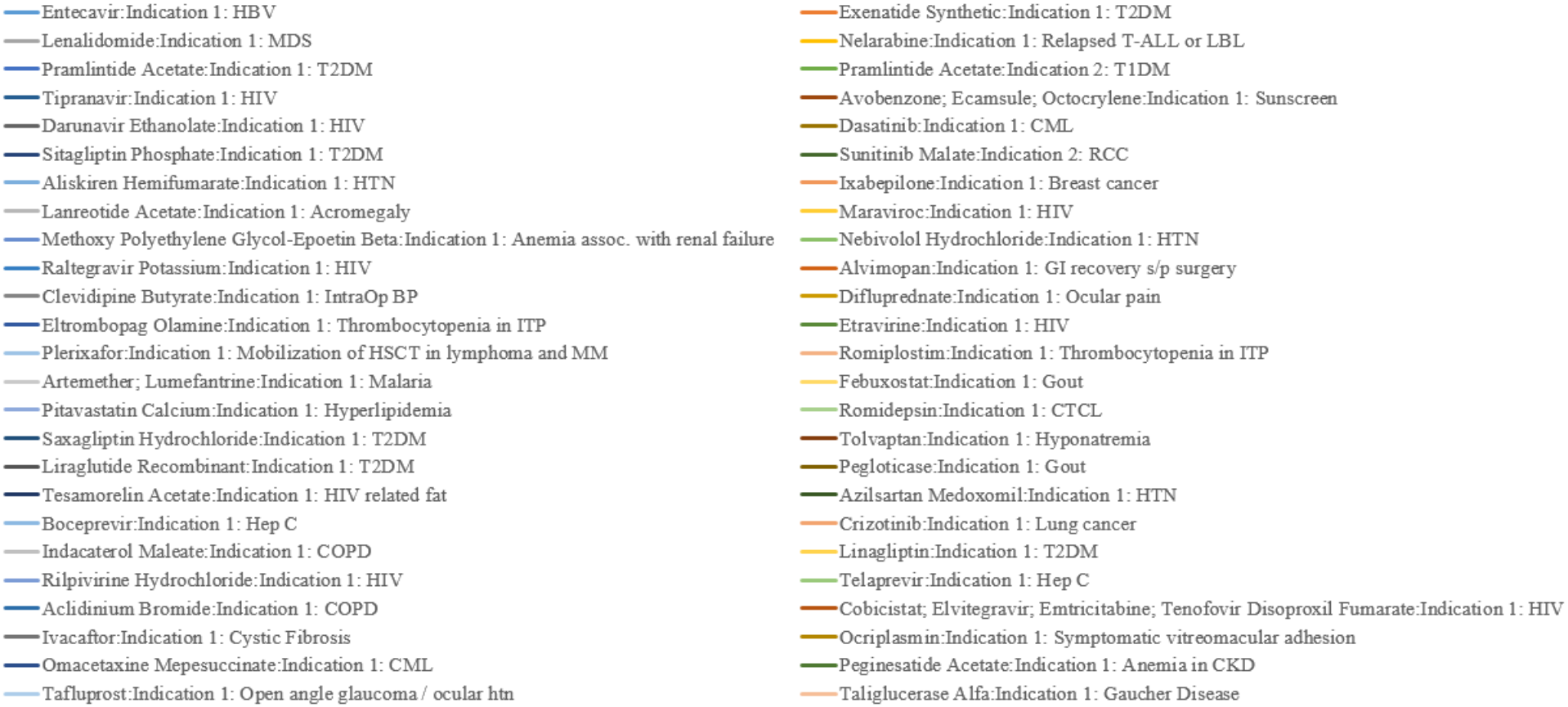
APPENDIX FIGURE 1. Cumulative comparative efficacy studies for each novel therapeutic approved by the Food and Drug Administration between 2005 and 2012 on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease as primary endpoints, or both ("single/surrogate"), by years since approval; (a) single pivotal approval studies, (b) surrogate approval studies, (c) single/surrogate approval studies. See color key below.

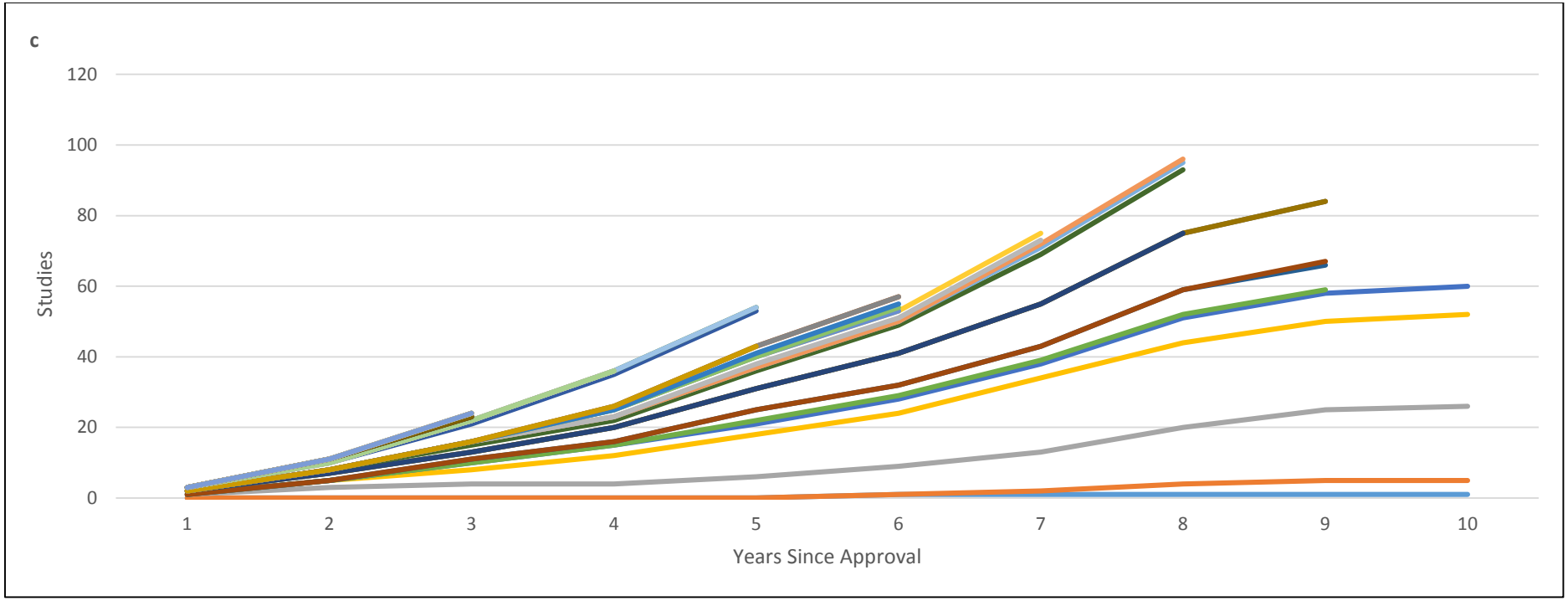
* Each year since approval estimated beginning at month-year of approval through following calendar year, with the final year concluding as of December 31, 2014 (the sample search cutoff date; thus, the final year may not represent a complete 12-month calendar year).

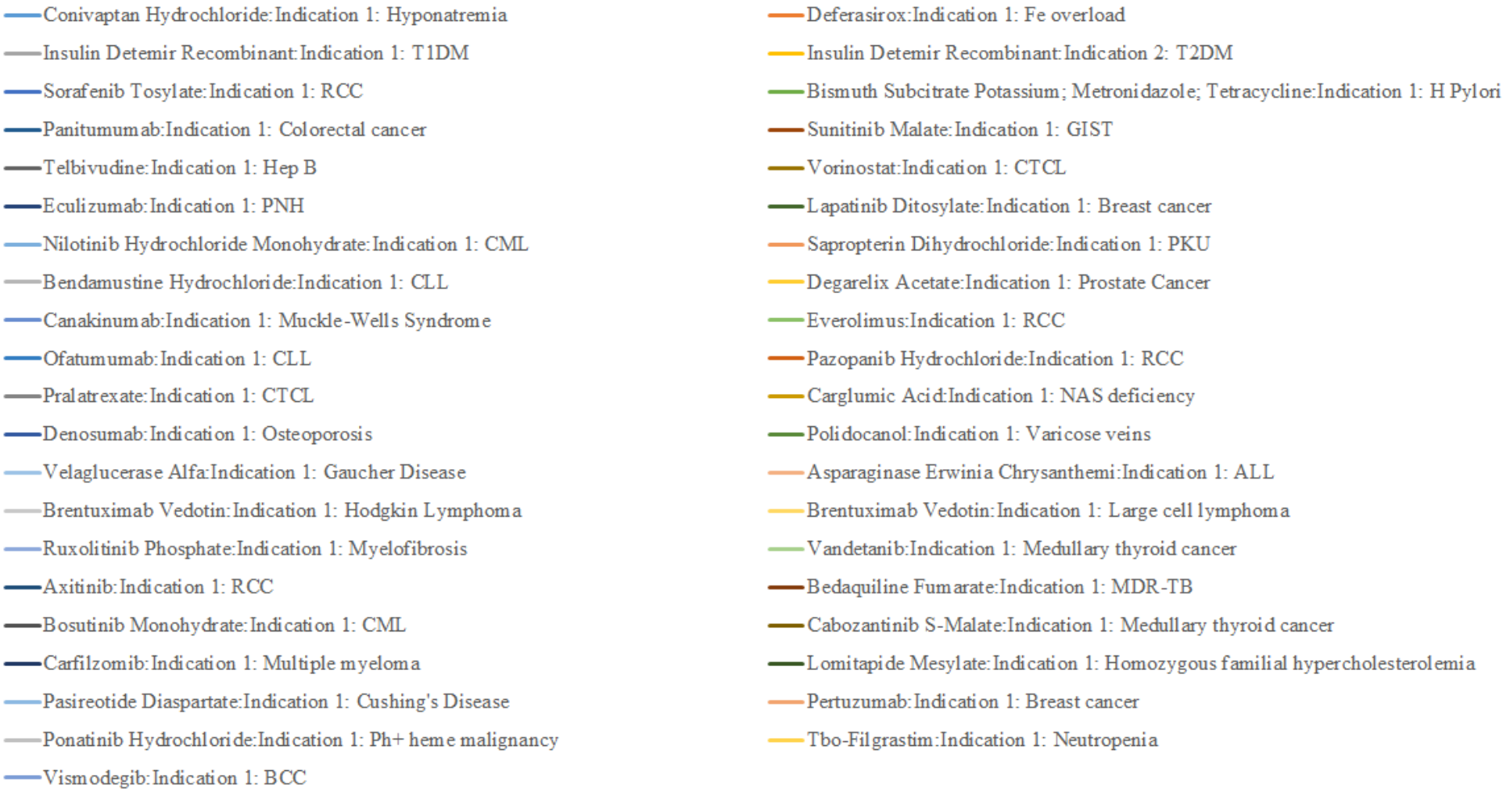



Galsulfase:Indication 1: Mucopolysaccharidosis VI
Mecasermin Rinfabate Recombinant:Indication 1: Growth failure
Alglucosidase Alfa:Indication 1: Pompe Disease
Anidulafungin:Indication 2: Esophageal candidiasis
Idursulfase:Indication 1: Hunter Syndrome
Temsirolimus:Indication 1: RCC
Dronedarone Hydrochloride:Indication 1: Antiarrhythmic for AFib
Golimumab:Indication 3: Ankylosing Spondylitis
Cabazitaxel:Indication 1: Prostate cancer
Eribulin Mesylate:Indication 1: Breast cancer
Incobotulinumtoxina:Indication 2: Cervical Dystonia
Clobazam:Indication 1: Lennox-Gastaut Syndrome
Ticagrelor:Indication 1: Platelet inhibition s/p MI angina
Apixaban:Indication 1: Prevention of stroke
Enzalutamide:Indication 1: Metastatic prostate cancer
Regorafenib:Indication 1: Metastatic CRC
Ziv-Aflibercept:Indication 1: Metastatic CRC
Mecasermin Recombinant:Indication 1: Growth failure
Micafungin Sodium:Indication 2: HSCT prophylaxis against candida
Anidulafungin:Indication 1: Candidemia
Decitabine:Indication 1: MDS
Retapamulin:Indication 1: Impetigo
Rilonacept:Indication 1:Familial Cold AutoInflam Syndrome
Golimumab:Indication 2: Psoriatic Arthritis
Prasugrel Hydrochloride:Indication 1: Platelet inhibitor s/p MI angina
Dabigatran Etexilate Mesylate:Indication 1: Stroke and PE in Afib
Incobotulinumtoxina:Indication 1: Blepharospasm
Abiraterone Acetate:Indication 1: Prostate cancer
Ipilimumab:Indication 1: Melanoma
Vemurafenib:Indication 1: Melanoma
Crofelemer:Indication 1:Diarrhea in HIV pts on ARV
Lucinactant:Indication 1: RDS
Teriflunomide:Indication 1: Relapsing MS


b
400
350
300
250
200
150
100
50
0
Studies
1
2
3
4
5
6
7
8
9
10
years Since Approval

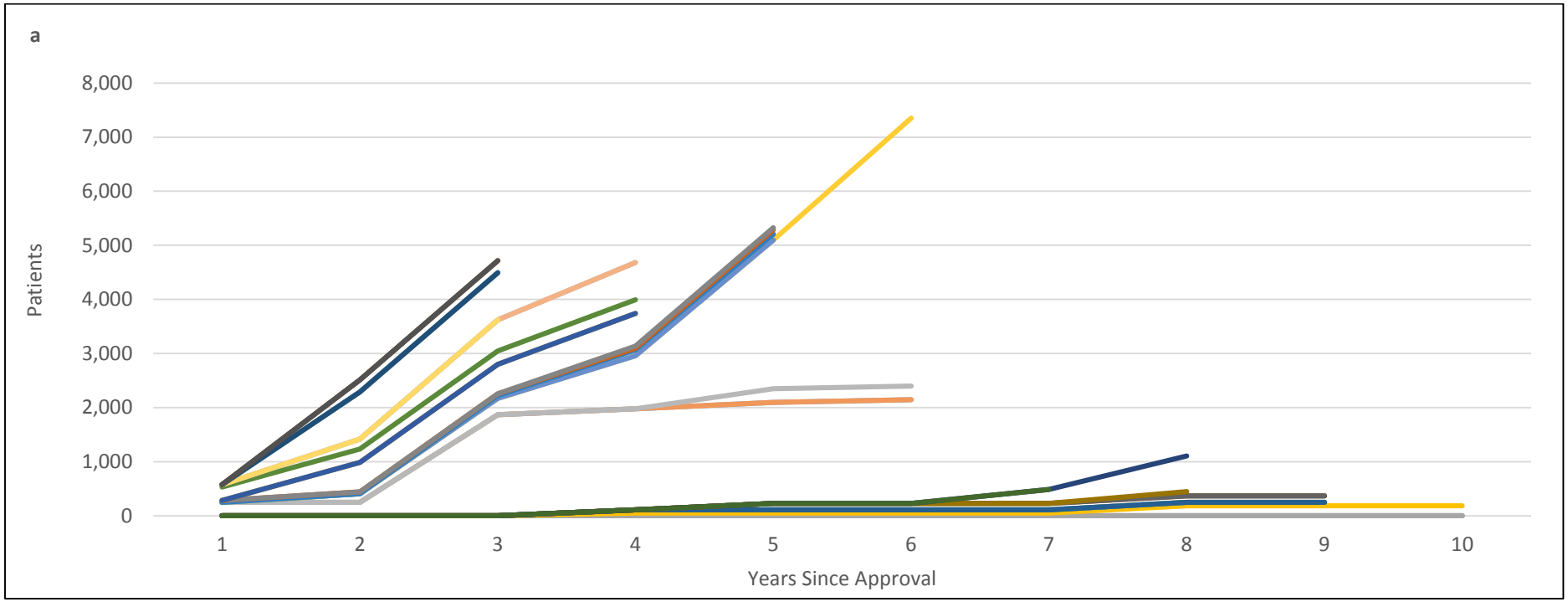

Entecavir:Indication 1: HBV
Lenalidomide:Indication 1: MDS
Pramlintide Acetate:Indication 1: T2DM
Tipranavir:Indication 1: HIV
Darunavir Ethanolate:Indication 1: HIV
Sitagliptin Phosphate:Indication 1: T2DM
Aliskiren Hemifumarate:Indication 1: HTN
Lanreotide Acetate:Indication 1: Acromegaly
Methoxy Polyethylene Glycol-Epoetin Beta:Indication 1: Anemia assoc. with renal failure
Raltegravir Potassium:Indication 1: HIV
Clevidipine Butyrate:Indication 1: IntraOp BP
Eltrombopag Olamine:Indication 1: Thrombocytopenia in ITP
Plerixafor:Indication 1: Mobilization of HSCT in lymphoma and MM
Artemether; Lumefantrine:Indication 1: Malaria
Pitavastatin Calcium:Indication 1: Hyperlipidemia
Saxagliptin Hydrochloride:Indication 1: T2DM
Liraglutide Recombinant:Indication 1: T2DM
Tesamorelin Acetate:Indication 1: HIV related fat
Boceprevir:Indication 1: Hep C
Indacaterol Maleate:Indication 1: COPD
Rilpivirine Hydrochloride:Indication 1: HIV
Aclidinium Bromide:Indication 1: COPD
Ivacaftor:Indication 1: Cystic Fibrosis
Omacetaxine Mepesuccinate:Indication 1: CML
Tafluprost:Indication 1: Open angle glaucoma / ocular htn
Exenatide Synthetic:Indication 1: T2DM
Nelarabine:Indication 1: Relapsed T-ALL or LBL
Pramlintide Acetate:Indication 2: T1DM
Avobenzone; Ecamsule; Octocrylene:Indication 1: Sunscreen
Dasatinib:Indication 1: CML
Sunitinib Malate:Indication 2: RCC
Ixabepilone:Indication 1: Breast cancer
Maraviroc:Indication 1: HIV
Nebivolol Hydrochloride:Indication 1: HTN
Alvimopan:Indication 1: GI recovery s/p surgery
Difluprednate:Indication 1: Ocular pain
Etravirine:Indication 1: HIV
Romiplostim:Indication 1: Thrombocytopenia in ITP
Febuxostat:Indication 1: Gout
Romidepsin:Indication 1: CTCL
Tolvaptan:Indication 1: Hyponatremia
Pegloticase:Indication 1: Gout
Azilsartan Medoxomil:Indication 1: HTN
Crizotinib:Indication 1: Lung cancer
Linagliptin:Indication 1: T2DM
Telaprevir:Indication 1: Hep C
Cobicistat; Elvitegravir; Emtricitabine; Tenofovir Disoproxil Fumarate:Indication 1: HIV
Ocriplasmin:Indication 1: Symptomatic vitreomacular adhesion
Peginesatide Acetate:Indication 1: Anemia in CKD
Taliglucerase Alfa:Indication 1: Gaucher Disease


c
120
100
80
60
40
20
0
Studies
1
2
3
4
5
6
7
8
9
10
Years Since Approval

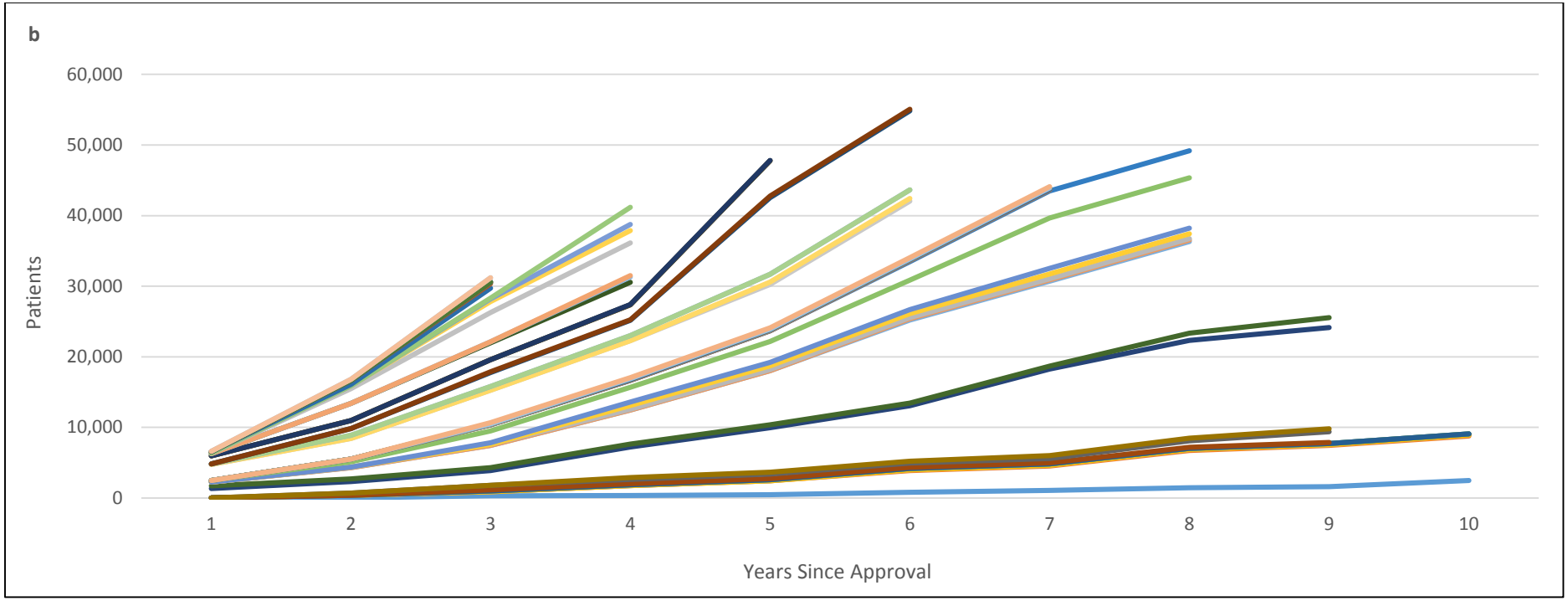

Conivaptan Hydrochloride:Indication 1: Hyponatremia
Insulin Detemir Recombinant:Indication 1: T1DM
Sorafenib Tosylate:Indication 1: RCC
Panitumumab:Indication 1: Colorectal cancer
Telbivudine:Indication 1: Hep B
Eculizumab:Indication 1: PNH
Nilotinib Hydrochloride Monohydrate:Indication 1: CML
Bendamustine Hydrochloride:Indication 1: CLL
Canakinumab:Indication 1: Muckle-Wells Syndrome
Ofatumumab:Indication 1: CLL
Pralatrexate:Indication 1: CTCL
Denosumab:Indication 1: Osteoporosis
Velaglucerase Alfa:Indication 1: Gaucher Disease
Brentuximab Vedotin:Indication 1: Hodgkin Lymphoma
Ruxolitinib Phosphate:Indication 1: Myelofibrosis
Axitinib:Indication 1: RCC
Bosutinib Monohydrate:Indication 1: CML
Carfilzomib:Indication 1: Multiple myeloma
Pasireotide Diaspartate:Indication 1: Cushing's Disease
Ponatinib Hydrochloride:Indication 1: Ph+ heme malignancy
Vismodegib:Indication 1: BCC
Deferasirox:Indication 1: Fe overload
Insulin Detemir Recombinant:Indication 2: T2DM
Bismuth Subcitrate Potassium; Metronidazole; Tetracycline:Indication 1: H Pylori
Sunitinib Malate:Indication 1: GIST
Vorinostat:Indication 1: CTCL
Lapatinib Ditosylate:Indication 1: Breast cancer
Sapropterin Dihydrochloride:Indication 1: PKU
Degarelix Acetate:Indication 1: Prostate Cancer
Everolimus:Indication 1: RCC
Pazopanib Hydrochloride:Indication 1: RCC
Carglumic Acid:Indication 1: NAS deficiency
Polidocanol:Indication 1: Varicose veins
Asparaginase Erwinia Chrysanthemi:Indication 1: ALL
Brentuximab Vedotin:Indication 1: Large cell lymphoma
Vandetanib:Indication 1: Medullary thyroid cancer
Bedaquiline Fumarate:Indication 1: MDR-TB
Cabozantinib S-Malate:Indication 1: Medullary thyroid cancer
Lomitapide Mesylate:Indication 1: Homozygous familial hypercholesterolemia
Pertuzumab:Indication 1: Breast cancer
Tbo-Filgrastim:Indication 1: Neutropenia

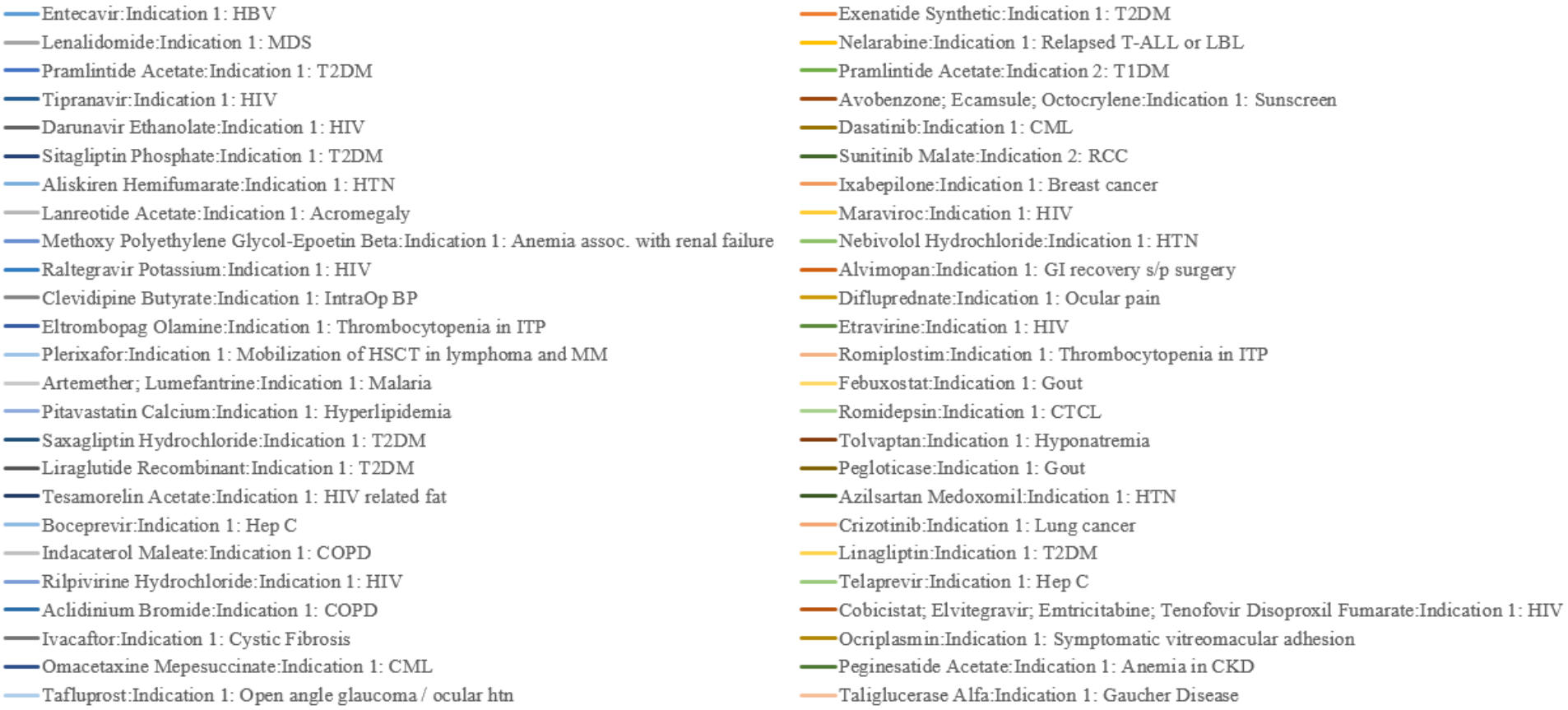
APPENDIX FIGURE 2. Cumulative intervention patients enrolled in comparative efficacy studies for each novel therapeutic approved by the Food and Drug Administration between 2005 and 2012 on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease as primary endpoints, or both ("single/surrogate"), by years since approval; (a) single pivotal approval patient enrollment, (b) surrogate approval patient enrollment, (c) single/surrogate approval patient enrollment. See color key below.

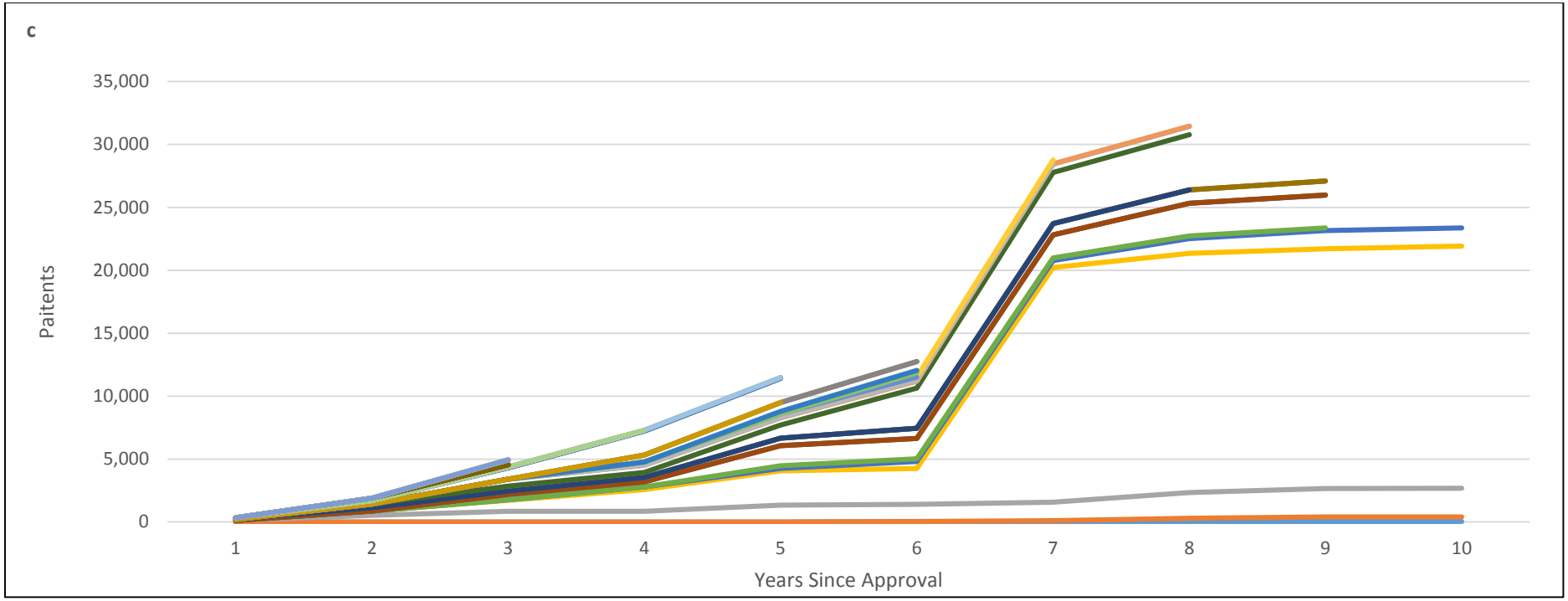
* Each year since approval estimated beginning at month-year of approval through following calendar year, with the final year concluding as of December 31, 2014 (the sample search cutoff date; thus, the final year may not represent a complete 12-month calendar year).




Galsulfase:Indication 1: Mucopolysaccharidosis VI
Mecasermin Rinfabate Recombinant:Indication 1: Growth failure
Alglucosidase Alfa:Indication 1: Pompe Disease
Anidulafungin:Indication 2: Esophageal candidiasis
Idursulfase:Indication 1: Hunter Syndrome
Temsirolimus:Indication 1: RCC
Dronedarone Hydrochloride:Indication 1: Antiarrhythmic for AFib
Golimumab:Indication 3: Ankylosing Spondylitis
Cabazitaxel:Indication 1: Prostate cancer
Eribulin Mesylate:Indication 1: Breast cancer
Incobotulinumtoxina:Indication 2: Cervical Dystonia
Clobazam:Indication 1: Lennox-Gastaut Syndrome
Ticagrelor:Indication 1: Platelet inhibition s/p MI angina
Apixaban:Indication 1: Prevention of stroke
Enzalutamide:Indication 1: Metastatic prostate cancer
Regorafenib:Indication 1: Metastatic CRC
Ziv-Aflibercept:Indication 1: Metastatic CRC
Mecasermin Recombinant:Indication 1: Growth failure
Micafungin Sodium:Indication 2: HSCT prophylaxis against candida
Anidulafungin:Indication 1: Candidemia
Decitabine:Indication 1: MDS
Retapamulin:Indication 1: Impetigo
Rilonacept:Indication 1:Familial Cold AutoInflam Syndrome
Golimumab:Indication 2: Psoriatic Arthritis
Prasugrel Hydrochloride:Indication 1: Platelet inhibitor s/p MI angina
Dabigatran Etexilate Mesylate:Indication 1: Stroke and PE in Afib
Incobotulinumtoxina:Indication 1: Blepharospasm
Abiraterone Acetate:Indication 1: Prostate cancer
Ipilimumab:Indication 1: Melanoma
Vemurafenib:Indication 1: Melanoma
Crofelemer:Indication 1:Diarrhea in HIV pts on ARV
Lucinactant:Indication 1: RDS
Teriflunomide:Indication 1: Relapsing MS


b
60,000
50,000
40,000
30,000
20,000
10,000
0
Patients
1
2
3
4
5
6
7
8
9
10
Years Since Approval

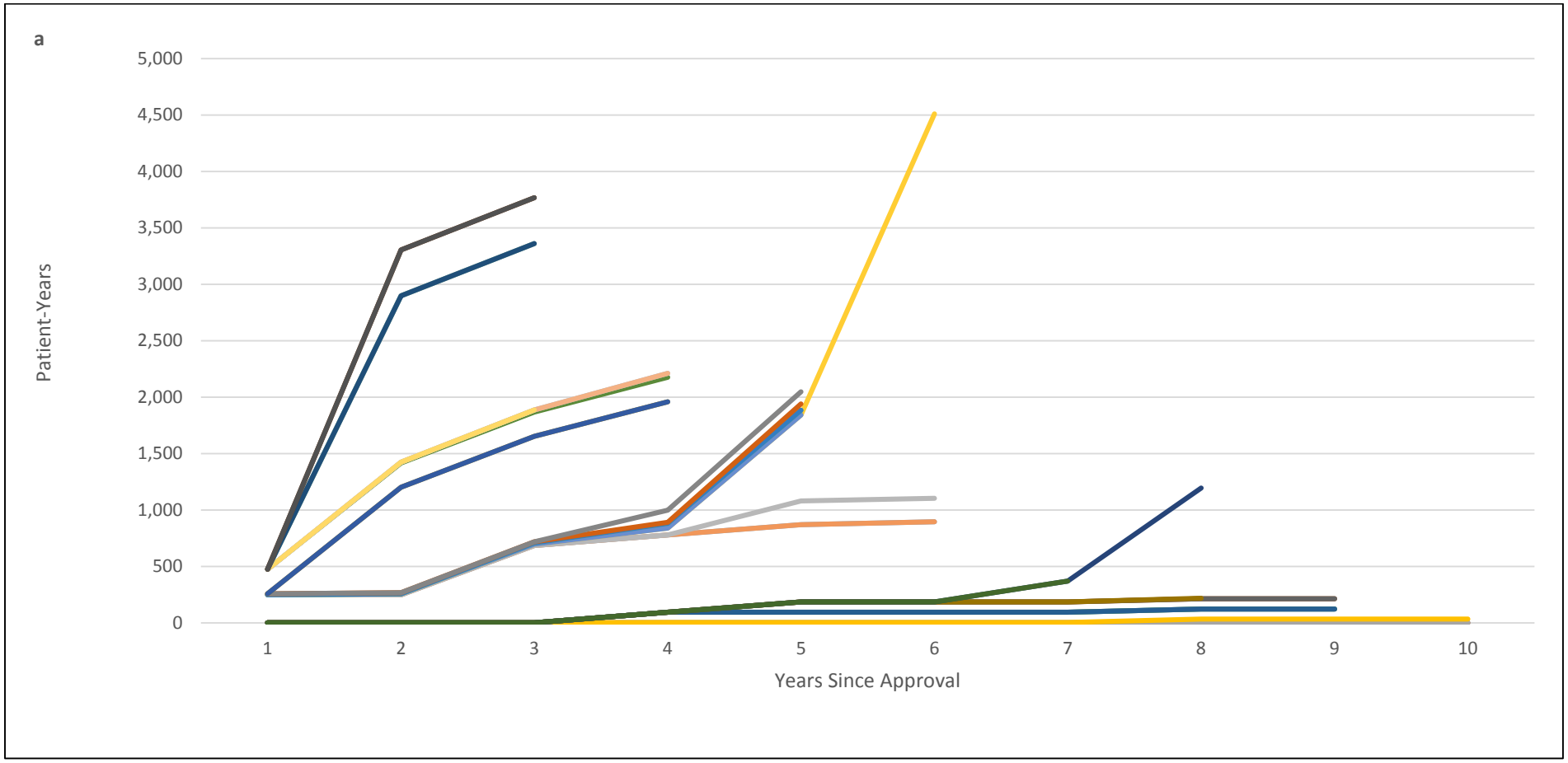

Entecavir:Indication 1: HBV
Lenalidomide:Indication 1: MDS
Pramlintide Acetate:Indication 1: T2DM
Tipranavir:Indication 1: HIV
Darunavir Ethanolate:Indication 1: HIV
Sitagliptin Phosphate:Indication 1: T2DM
Aliskiren Hemifumarate:Indication 1: HTN
Lanreotide Acetate:Indication 1: Acromegaly
Methoxy Polyethylene Glycol-Epoetin Beta:Indication 1: Anemia assoc. with renal failure
Raltegravir Potassium:Indication 1: HIV
Clevidipine Butyrate:Indication 1: IntraOp BP
Eltrombopag Olamine:Indication 1: Thrombocytopenia in ITP
Plerixafor:Indication 1: Mobilization of HSCT in lymphoma and MM
Artemether; Lumefantrine:Indication 1: Malaria
Pitavastatin Calcium:Indication 1: Hyperlipidemia
Saxagliptin Hydrochloride:Indication 1: T2DM
Liraglutide Recombinant:Indication 1: T2DM
Tesamorelin Acetate:Indication 1: HIV related fat
Boceprevir:Indication 1: Hep C
Indacaterol Maleate:Indication 1: COPD
Rilpivirine Hydrochloride:Indication 1: HIV
Aclidinium Bromide:Indication 1: COPD
Ivacaftor:Indication 1: Cystic Fibrosis
Omacetaxine Mepesuccinate:Indication 1: CML
Tafluprost:Indication 1: Open angle glaucoma / ocular htn
Exenatide Synthetic:Indication 1: T2DM
Nelarabine:Indication 1: Relapsed T-ALL or LBL
Pramlintide Acetate:Indication 2: T1DM
Avobenzone; Ecamsule; Octocrylene:Indication 1: Sunscreen
Dasatinib:Indication 1: CML
Sunitinib Malate:Indication 2: RCC
Ixabepilone:Indication 1: Breast cancer
Maraviroc:Indication 1: HIV
Nebivolol Hydrochloride:Indication 1: HTN
Alvimopan:Indication 1: GI recovery s/p surgery
Difluprednate:Indication 1: Ocular pain
Etravirine:Indication 1: HIV
Romiplostim:Indication 1: Thrombocytopenia in ITP
Febuxostat:Indication 1: Gout
Romidepsin:Indication 1: CTCL
Tolvaptan:Indication 1: Hyponatremia
Pegloticase:Indication 1: Gout
Azilsartan Medoxomil:Indication 1: HTN
Crizotinib:Indication 1: Lung cancer
Linagliptin:Indication 1: T2DM
Telaprevir:Indication 1: Hep C
Cobicistat; Elvitegravir; Emtricitabine; Tenofovir Disoproxil Fumarate:Indication 1: HIV
Ocriplasmin:Indication 1: Symptomatic vitreomacular adhesion
Peginesatide Acetate:Indication 1: Anemia in CKD
Taliglucerase Alfa:Indication 1: Gaucher Disease

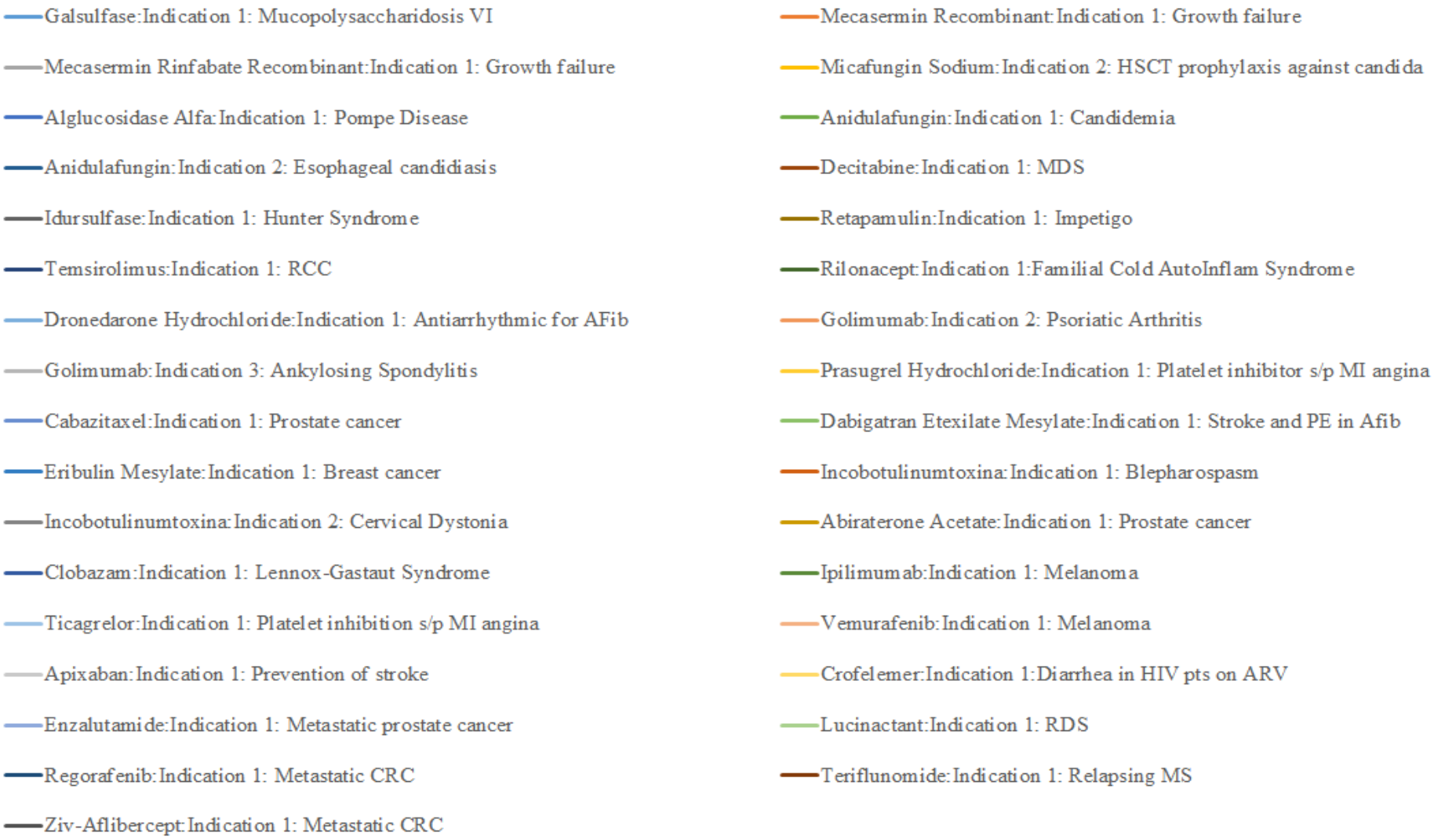

c
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
Paitents
1
2
3
4
5
6
7
8
9
10
Years Since Approval

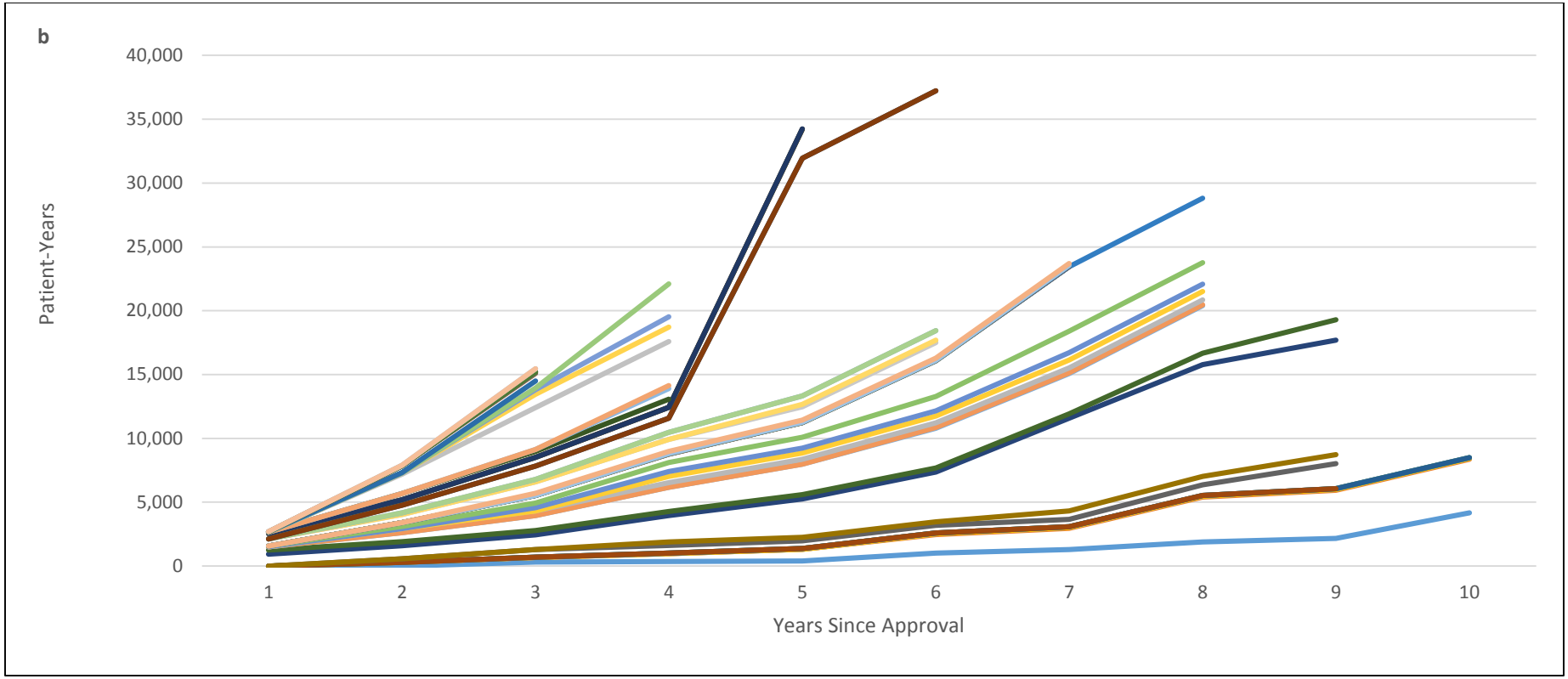

Conivaptan Hydrochloride:Indication 1: Hyponatremia
Insulin Detemir Recombinant:Indication 1: T1DM
Sorafenib Tosylate:Indication 1: RCC
Panitumumab:Indication 1: Colorectal cancer
Telbivudine:Indication 1: Hep B
Eculizumab:Indication 1: PNH
Nilotinib Hydrochloride Monohydrate:Indication 1: CML
Bendamustine Hydrochloride:Indication 1: CLL
Canakinumab:Indication 1: Muckle-Wells Syndrome
Ofatumumab:Indication 1: CLL
Pralatrexate:Indication 1: CTCL
Denosumab:Indication 1: Osteoporosis
Velaglucerase Alfa:Indication 1: Gaucher Disease
Brentuximab Vedotin:Indication 1: Hodgkin Lymphoma
Ruxolitinib Phosphate:Indication 1: Myelofibrosis
Axitinib:Indication 1: RCC
Bosutinib Monohydrate:Indication 1: CML
Carfilzomib:Indication 1: Multiple myeloma
Pasireotide Diaspartate:Indication 1: Cushing's Disease
Ponatinib Hydrochloride:Indication 1: Ph+ heme malignancy
Vismodegib:Indication 1: BCC
Deferasirox:Indication 1: Fe overload
Insulin Detemir Recombinant:Indication 2: T2DM
Bismuth Subcitrate Potassium; Metronidazole; Tetracycline:Indication 1: H Pylori
Sunitinib Malate:Indication 1: GIST
Vorinostat:Indication 1: CTCL
Lapatinib Ditosylate:Indication 1: Breast cancer
Sapropterin Dihydrochloride:Indication 1: PKU
Degarelix Acetate:Indication 1: Prostate Cancer
Everolimus:Indication 1: RCC
Pazopanib Hydrochloride:Indication 1: RCC
Carglumic Acid:Indication 1: NAS deficiency
Polidocanol:Indication 1: Varicose veins
Asparaginase Erwinia Chrysanthemi:Indication 1: ALL
Brentuximab Vedotin:Indication 1: Large cell lymphoma
Vandetanib:Indication 1: Medullary thyroid cancer
Bedaquiline Fumarate:Indication 1: MDR-TB
Cabozantinib S-Malate:Indication 1: Medullary thyroid cancer
Lomitapide Mesylate:Indication 1: Homozygous familial hypercholesterolemia
Pertuzumab:Indication 1: Breast cancer
Tbo-Filgrastim:Indication 1: Neutropenia

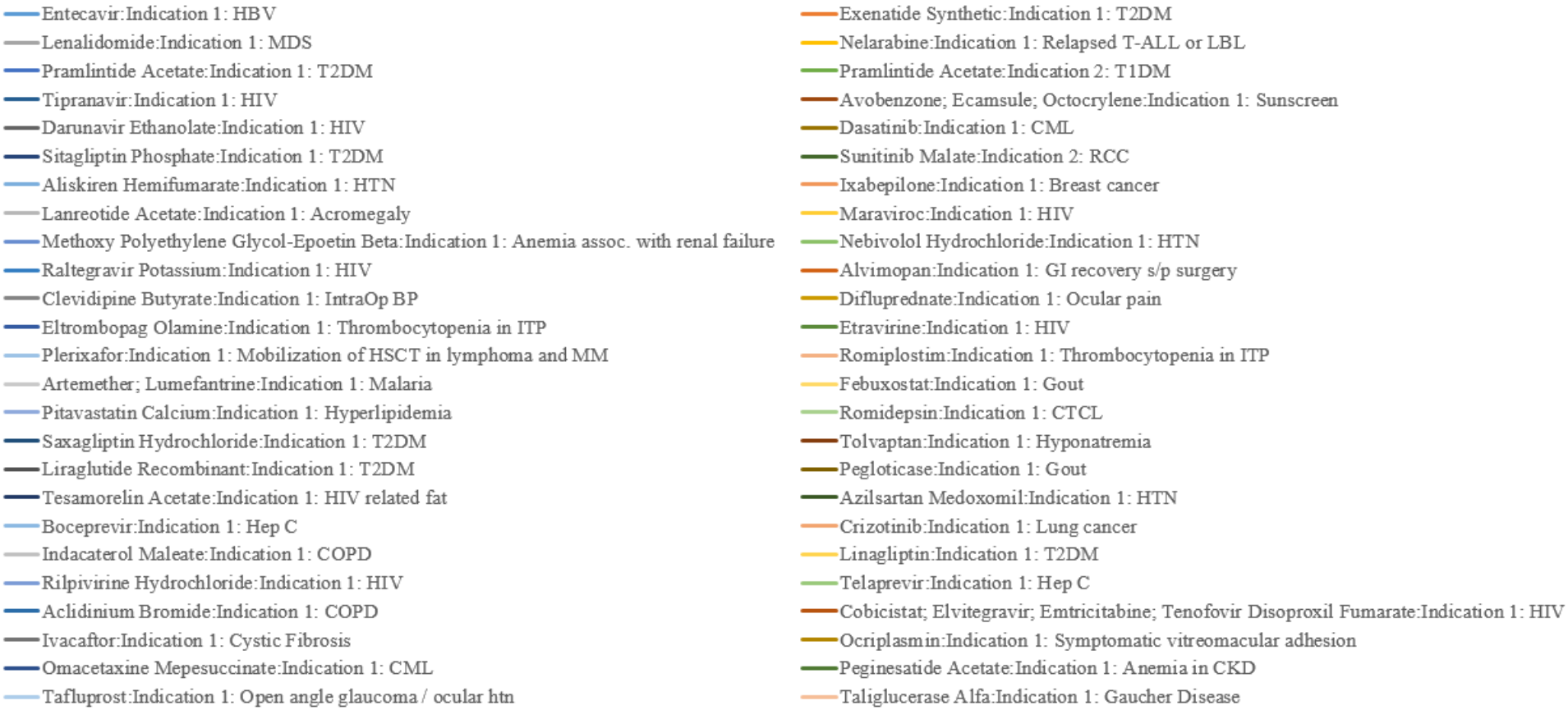
APPENDIX FIGURE 3: Cumulative intervention patient-years exposure among patients enrolled in in comparative efficacy studies for each novel therapeutic approved by the Food and Drug Administration between 2005 and 2012 on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease as primary endpoints, or both ("single/surrogate"), by years since approval; (a) single pivotal approval patient-years exposure, (b) surrogate approval patient-years exposure, (c) single/surrogate approval patient-years exposure.

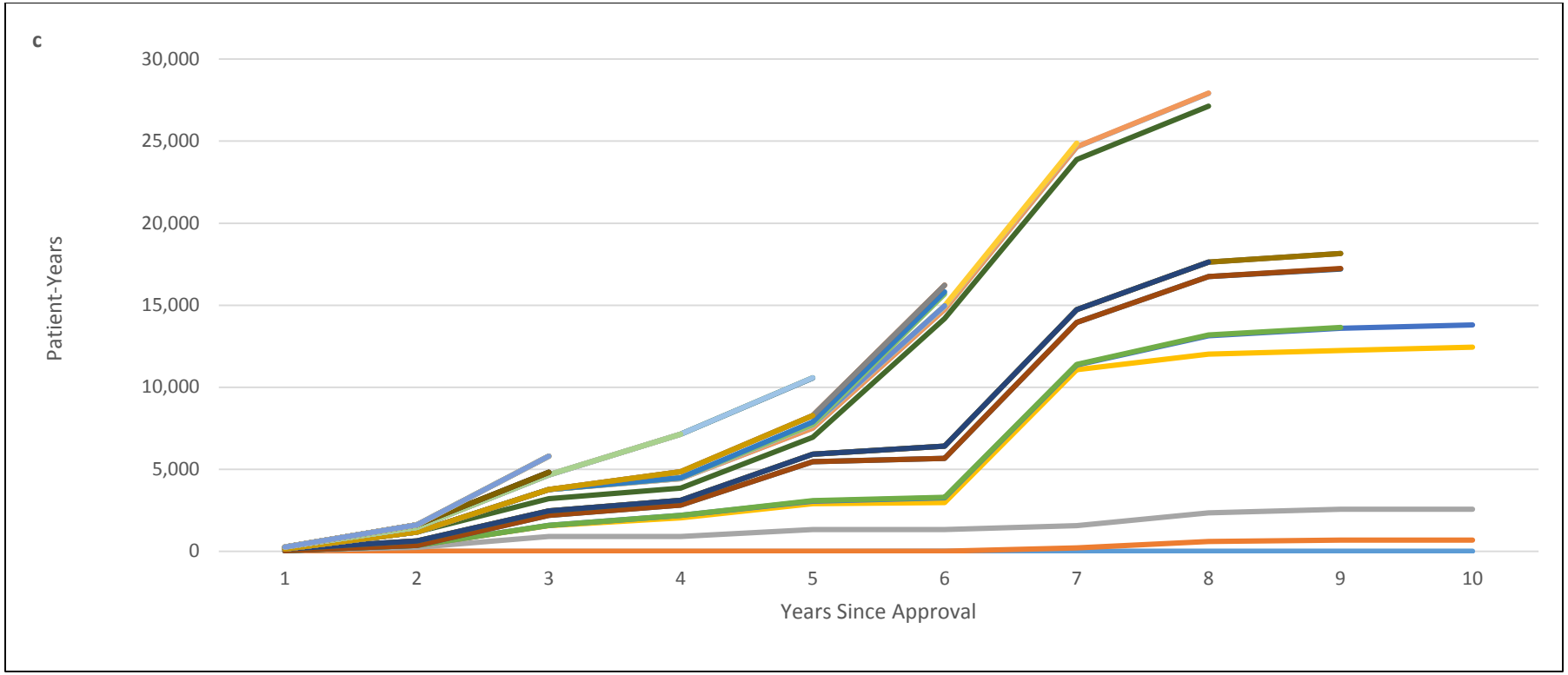
* Each year since approval estimated beginning at month-year of approval through following calendar year, with the final year concluding as of December 31, 2014 (the sample search cutoff date; thus, the final year may not represent a complete 12-month calendar year).

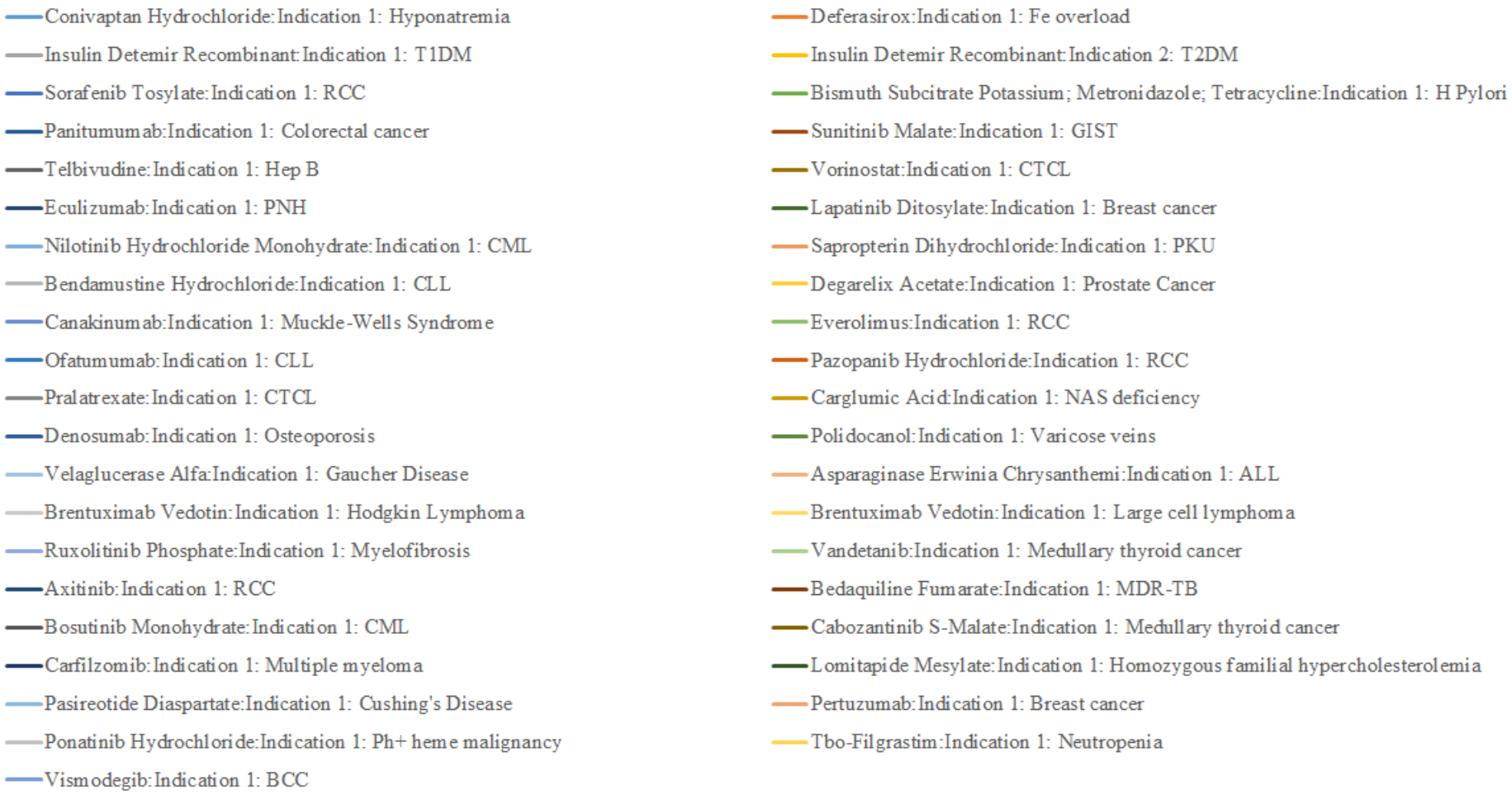



Galsulfase:Indication 1: Mucopolysaccharidosis VI
Mecasermin Rinfabate Recombinant:Indication 1: Growth failure
Alglucosidase Alfa:Indication 1: Pompe Disease
Anidulafungin:Indication 2: Esophageal candidiasis
Idursulfase:Indication 1: Hunter Syndrome
Temsirolimus:Indication 1: RCC
Dronedarone Hydrochloride:Indication 1: Antiarrhythmic for AFib
Golimumab:Indication 3: Ankylosing Spondylitis
Cabazitaxel:Indication 1: Prostate cancer
Eribulin Mesylate:Indication 1: Breast cancer
Incobotulinumtoxina:Indication 2: Cervical Dystonia
Clobazam:Indication 1: Lennox-Gastaut Syndrome
Ticagrelor:Indication 1: Platelet inhibition s/p MI angina
Apixaban:Indication 1: Prevention of stroke
Enzalutamide:Indication 1: Metastatic prostate cancer
Regorafenib:Indication 1: Metastatic CRC
Ziv-Aflibercept:Indication 1: Metastatic CRC
Mecasermin Recombinant:Indication 1: Growth failure
Micafungin Sodium:Indication 2: HSCT prophylaxis against candida
Anidulafungin:Indication 1: Candidemia
Decitabine:Indication 1: MDS
Retapamulin:Indication 1: Impetigo
Rilonacept:Indication 1:Familial Cold AutoInflam Syndrome
Golimumab:Indication 2: Psoriatic Arthritis
Prasugrel Hydrochloride:Indication 1: Platelet inhibitor s/p MI angina
Dabigatran Etexilate Mesylate:Indication 1: Stroke and PE in Afib
Incobotulinumtoxina:Indication 1: Blepharospasm
Abiraterone Acetate:Indication 1: Prostate cancer
Ipilimumab:Indication 1: Melanoma
Vemurafenib:Indication 1: Melanoma
Crofelemer:Indication 1:Diarrhea in HIV pts on ARV
Lucinactant:Indication 1: RDS
Teriflunomide:Indication 1: Relapsing MS


b
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
Patient-Years
1
2
3
4
5
6
7
8
9
10
Years Since Approval


Entecavir:Indication 1: HBV
Lenalidomide:Indication 1: MDS
Pramlintide Acetate:Indication 1: T2DM
Tipranavir:Indication 1: HIV
Darunavir Ethanolate:Indication 1: HIV
Sitagliptin Phosphate:Indication 1: T2DM
Aliskiren Hemifumarate:Indication 1: HTN
Lanreotide Acetate:Indication 1: Acromegaly
Methoxy Polyethylene Glycol-Epoetin Beta:Indication 1: Anemia assoc. with renal failure
Raltegravir Potassium:Indication 1: HIV
Clevidipine Butyrate:Indication 1: IntraOp BP
Eltrombopag Olamine:Indication 1: Thrombocytopenia in ITP
Plerixafor:Indication 1: Mobilization of HSCT in lymphoma and MM
Artemether; Lumefantrine:Indication 1: Malaria
Pitavastatin Calcium:Indication 1: Hyperlipidemia
Saxagliptin Hydrochloride:Indication 1: T2DM
Liraglutide Recombinant:Indication 1: T2DM
Tesamorelin Acetate:Indication 1: HIV related fat
Boceprevir:Indication 1: Hep C
Indacaterol Maleate:Indication 1: COPD
Rilpivirine Hydrochloride:Indication 1: HIV
Aclidinium Bromide:Indication 1: COPD
Ivacaftor:Indication 1: Cystic Fibrosis
Omacetaxine Mepesuccinate:Indication 1: CML
Tafluprost:Indication 1: Open angle glaucoma / ocular htn
Exenatide Synthetic:Indication 1: T2DM
Nelarabine:Indication 1: Relapsed T-ALL or LBL
Pramlintide Acetate:Indication 2: T1DM
Avobenzone; Ecamsule; Octocrylene:Indication 1: Sunscreen
Dasatinib:Indication 1: CML
Sunitinib Malate:Indication 2: RCC
Ixabepilone:Indication 1: Breast cancer
Maraviroc:Indication 1: HIV
Nebivolol Hydrochloride:Indication 1: HTN
Alvimopan:Indication 1: GI recovery s/p surgery
Difluprednate:Indication 1: Ocular pain
Etravirine:Indication 1: HIV
Romiplostim:Indication 1: Thrombocytopenia in ITP
Febuxostat:Indication 1: Gout
Romidepsin:Indication 1: CTCL
Tolvaptan:Indication 1: Hyponatremia
Pegloticase:Indication 1: Gout
Azilsartan Medoxomil:Indication 1: HTN
Crizotinib:Indication 1: Lung cancer
Linagliptin:Indication 1: T2DM
Telaprevir:Indication 1: Hep C
Cobicistat; Elvitegravir; Emtricitabine; Tenofovir Disoproxil Fumarate:Indication 1: HIV
Ocriplasmin:Indication 1: Symptomatic vitreomacular adhesion
Peginesatide Acetate:Indication 1: Anemia in CKD
Taliglucerase Alfa:Indication 1: Gaucher Disease


c
30,000
25,000
20,000
15,000
10,000
5,000
0
Patient-Years
1
2
3
4
5
6
7
8
9
10
Years Since Approval


Conivaptan Hydrochloride:Indication 1: Hyponatremia
Insulin Detemir Recombinant:Indication 1: T1DM
Sorafenib Tosylate:Indication 1: RCC
Panitumumab:Indication 1: Colorectal cancer
Telbivudine:Indication 1: Hep B
Eculizumab:Indication 1: PNH
Nilotinib Hydrochloride Monohydrate:Indication 1: CML
Bendamustine Hydrochloride:Indication 1: CLL
Canakinumab:Indication 1: Muckle-Wells Syndrome
Ofatumumab:Indication 1: CLL
Pralatrexate:Indication 1: CTCL
Denosumab:Indication 1: Osteoporosis
Velaglucerase Alfa:Indication 1: Gaucher Disease
Brentuximab Vedotin:Indication 1: Hodgkin Lymphoma
Ruxolitinib Phosphate:Indication 1: Myelofibrosis
Axitinib:Indication 1: RCC
Bosutinib Monohydrate:Indication 1: CML
Carfilzomib:Indication 1: Multiple myeloma
Pasireotide Diaspartate:Indication 1: Cushing's Disease
Ponatinib Hydrochloride:Indication 1: Ph+ heme malignancy
Vismodegib:Indication 1: BCC
Deferasirox:Indication 1: Fe overload
Insulin Detemir Recombinant:Indication 2: T2DM
Bismuth Subcitrate Potassium; Metronidazole; Tetracycline:Indication 1: H Pylori
Sunitinib Malate:Indication 1: GIST
Vorinostat:Indication 1: CTCL
Lapatinib Ditosylate:Indication 1: Breast cancer
Sapropterin Dihydrochloride:Indication 1: PKU
Degarelix Acetate:Indication 1: Prostate Cancer
Everolimus:Indication 1: RCC
Pazopanib Hydrochloride:Indication 1: RCC
Carglumic Acid:Indication 1: NAS deficiency
Polidocanol:Indication 1: Varicose veins
Asparaginase Erwinia Chrysanthemi:Indication 1: ALL
Brentuximab Vedotin:Indication 1: Large cell lymphoma
Vandetanib:Indication 1: Medullary thyroid cancer
Bedaquiline Fumarate:Indication 1: MDR-TB
Cabozantinib S-Malate:Indication 1: Medullary thyroid cancer
Lomitapide Mesylate:Indication 1: Homozygous familial hypercholesterolemia
Pertuzumab:Indication 1: Breast cancer
Tbo-Filgrastim:Indication 1: Neutropenia