Original Article

Trends in FDA drug approvals over last 2 decades: An observational study

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Abstract

Introduction: The discovery of novel drugs is critical for pharmaceutical research and development as well as for patient treatment. Repurposing existing drugs that may have anticipated effects as potential candidate is one way to meet this important goal. Systematic investigation and comprehensive analysis of approved drugs could provide valuable insights into trends in the discovery and may contribute to further discovery of newer drugs systematically. Food and drug administration (FDA's) Center for Drug Evaluation and Research (CDER) every year summarizes novel drugs, some of which are truly innovative and help in advancing clinical care. This study was conducted to find a trend in drug approvals by FDA in the last 2 decades. Awareness of these new drugs amongst the primary care physicians is also crucial as they have been prescribing these agents in the past. **Methodology:** In this cross-sectional study, we collected, surveyed, and analyzed drugs approved by U.S. Food and Drug Administration (USFDA) from the year 2000 till 2017 identified from ClinicalTrials.gov and online database of FDA. Drugs approved every year were assessed for total number, class of drug, indication, and category of approval. Type of accelerated regulatory pathways and reasons for speedy approvals every year were also studied. Microsoft Office Excel 2007 was used for tabulation and analysis. **Results:** Total 209 were approved from 2000 to 2008. Out of these 9.09% were indicated for cardiovascular disorders and 12.91% for neurological disorders. Antibiotics (5.26%) and antivirals (5.74%) were least contributed, whereas anticancer drugs (11.96%) and biologics (7.17%) approval remained constant. Whereas, out of three hundred and two drugs approved during 2009--2017, 5.29% were for cardiovascular disorders, 9.93% for neurological disorders. Antibiotics (5.29%) and antivirals (5.96%) were least in number, whereas anticancer drugs (17.54%) and biologics (15.56%) approval took a steep rise in these years. Also, a wide variation in the number and category of approval was observed over a period of years. The use of fast track, accelerated approval, and priority review programs have also been steadily increasing since 2000. **Conclusion:** There has been a steady rate of introduction of new drugs by CDER over the last two decades. Expedited approval of anticancer and biologics is seen as recent trend in drug development. Relatively, slow progress in approval of drugs for neurological disorders (depression, psychosis, multiple sclerosis, etc.) and lifestyle diseases like obesity, atherosclerosis, diabetes, etc., were seen. These findings reflect more emphasis being laid down in research for anticancer drugs and biologics.

Keywords: Drug approval, drug discovery and development, USFDA

History and Introduction

Since its inception as a Food and Drug Administration (FDA) in 1930, FDA is serving as a gatekeeper for promoting safe and effective drugs. After 1962 Amendments to the federal Food Drug and Cosmetic Act (FD and C), well-controlled trial became standard of evidence which contributed to evaluation of new drugs in terms of efficacy and safety.[1,2]

First federal drug law was passed by Congress in 1906 which prohibited misbranded and adulterated drugs apart from foods and drinks.[1] Then in 1938, Congress passed the federal which ensures that drug is safe before entering the market.[1] After Kefauver--Harris Drug Amendment in 1962, not only safety,

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but efficacy also became an important parameter before market authorization.[3] In 1966, the drug division of FDA mentioned in FD and C Act was reorganized to office of new drugs which started reviewing new drug applications.[2] In 1982, bureau of biologics was merged with it. In 1987, two different entities Center for Drug Evaluation and Research (CDER) and Centre for Biologics and Evaluation Research (CBER) were formed.[4] Originally; CDER was composed of six offices, now CDER is comprised of 13 offices. Today, CDER is serving as a consumer watchdog for thousands of drugs available in the market by supporting innovation and thereby improving treatment for patients.

Other notable milestones was Orphan drug Act, 1983 which encourages research and development of drugs for rare diseases.[1] This act also offers financial incentive, tax credits for clinical research cost for 7 years of marketing exclusivity. Access to generic prescribing became an important area to cut down the cost for common man. The 1984 act (Hatch--Waxman Act) encourages production of generics while protecting rights of brand name manufacturers.[2] In 1999, Clinical Trials.gov was formed to give information of recent clinical research to patients regarding ongoing promising therapies.[2] In 2004, "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products" was released by FDA which highlighted collective action needed to transform the development, evaluation, and manufacture of medical products.[1,2] Since then, consistent reformations have been incorporated as per requirements and patient safety.

Seeing rapid drug approvals in the recent years, we planned to study the trends in novel drug approvals by FDA over the past 18 years and evaluate reasons for the same. Also, knowledge of these novel agents is prudent for primary care physicians who under the influence of key opinion leaders are adopting and prescribing these drugs.

Methodology

Data for the study were collected from online database of FDA under the category of novel drug approvals from the year 2000 till 2017. CDER issues an annual report which gives a list of all new drugs approved during a particular year. Also, any new indication of an already FDA approved drug is mentioned.

All the drugs listed in the drug summary of respective year were segregated for parameters: Number of drug approved per year, pharmaceutical class of drug, indication for use in patient population, and type of approval received or combined expedited approvals.

Also, literature search was conducted in electronic databases like PubMed, clinicaltrials.gov, Google scholar, and Cochrane database to corroborate evidence which led to approval of drugs.

Statistical analysis

Data were entered in MS Excel sheet 2007 for tabulation and analysis. Descriptive statistics was used for analysis.

Results

Trends in drug approval in last 18 years are as follows

2000--2008: A total number of drugs approved were 209. Out of these, 9.09% of drugs like fondaparinux, ranolazine, etc., were indicated for cardiovascular disorders. 12.91% of drugs were approved for neurological disorders namely rivastigmine, aripiprazole, etc., Antibiotics (5.26%) and antivirals (5.74%) were least contributed, anticancer drugs (11.96%) and biologics (7.17%) approval remained constant during these years.[5] These results reflect that less number of Investigational New Drug Applications (INDA) are being filed pertaining to antibiotic/antiviral category. It could be because of research and developments of pharmaceutical giants are focused on other categories of drugs or failure of New Chemical Entity (NCE) during development. Some landmark drugs during this period are mentioned in Table 1.

2009--2017: Total number of drugs approved was 302. Out of these, 5.29% of drugs like prasugrel, rivaroxaban, etc., were indicated for cardiovascular disorders. This is relatively less as compared to previous years, i.e. a fall of 4% approximately. 9.93% of drugs were indicated for neurological disorders namely perampanel, pimavanserine, etc. In neurological indications, again a fall of 3% approximately is observed as compared to previous years. Antibiotics (5.29%) and antivirals (5.96%) were least contributed, whereas anticancer drugs (17.54%) and biologics (15.56%) approval took a steep rise. Some important drugs approved during these years are highlighted in Table 2. We observed that limited numbers of drugs are being approved for lifestyle disorders like diabetes, obesity, cardiovascular disorders, etc., Presently, more number of anticancer drugs and biologics are being approved compared to drugs required for lifestyle diseases, antibiotics, respiratory disorders, etc.

Is it discovery-driven or market-driven approach?? The answer to this query is difficult to decipher. Number of new cancer patients will rise to 23.6 million by 2030. In 2018 alone, estimated 1,735,350 new cancer patients were diagnosed in U.S. and 609,640 people have died.[6] Diabetes is not behind in the race. There will be 54% rise in number of diabetic patients in America by 2030 and total deaths due to diabetes will be increased by 38%. Annual and societal costs will reach to $622 billion by 2030.[7] Table 3, 4 and 5 highlights list of anticancer drugs, biologics, and antiviral drugs approved, respectively.

The driving force to this increase in new drug approvals can be attributed to a number of factors:

1. Increased New Drug Applications

The number of New Drug Applications (NDA's)/Biologic License Applications (BLA's) filed per year has increased slightly over the past decade. Between 2000 and 2010, an average of 23 approvals was made per year, compared with 35 approvals in 2011, 39 in 2012, 45 in 2015, and 46 in 2017. 59 novel agents

Table 1: List of some landmark drugs between 2000 and 2010

Year	Drug	Indication	Review type
2000	Linezolid	Skin and skin structure infections	P
	Insulin glargine	DM-1	S
	Insulin aspart	DM-1	S
	Bivalirudin	Unstable angina in patients undergoing PTCA	S
	Oxcarbazepine	Partial seizures	S
	Rivastigmine tartarate	Alzheimer's dementia	S
2001	Fondaparinux sodium	Prophylaxis of DVT	P
	Ziprasidone HCL	Schizophrenia	S
2002	Voriconazole	Invasive aspergillosis	S
	Fulvestrant	Metastatic breast carcinoma	S
	Oxaliplatin	Metastatic carcinoma of colon or rectum	P
	Ezetimibe	Primary hypercholesterolemia	S
	Aripiprazole	Schizophrenia	S
2003	Gefitinib	Metastatic nonsmall cell lung carcinoma	P
	Bortezomib	Multiple myeloma	P, O
	Aprepitant	CINV	P
	Rosuvastatin calcium	Primary hypercholesterolemia	S
	Memantine HCL	Alzheimer's type dementia	S
2004	Pemetrexed Disodium	Malignant pleural mesothelioma	P, O
	Azacitidine	Myelodysplastic syndrome and CML	P, O
	Cetuximab	Colorectal carcinoma	P
	Bevacizumab	Metastatic carcinoma of the colon and rectum	P
2005	Insulin detemir	DM-1&2	S
2006	Decitabine	Myelodysplastic syndrome	S, O
	Varenicline	Smoking cessation	P
	Ranolazine	Chronic angina	S
2007	Nebivolol	Hypertension	S
2008	Romiplostim	ITP	P, O
	Silodosin	BHP	S
2009	Artemether 20 mg lumefantrine 120 mg	Malaria	P, O
2010	Dabigatran etexilate mesylate	Stroke in patients of atrial fibrillation	P

P - Priority review, S - Standard review, O - Orphan designation. Standard Review -Products that do not qualify for priority review

have been approved in 2018.[8] (An application may have been filed in 1 year and approved in another). An increase in the number of new drug filings could potentially affect the number of approvals in a given year. Figure 1 depicts the total number of new drugs approved every year.

2. First in Class and Orphan Approvals

In recent years, there has also been a shift in the types of new drugs that are submitted to the FDA for approval: CDER had

Table 2: List of some landmark drugs between 2011 and 2018

Year	Drug	Indication	Review type
2011	Rivaroxaban	To decrease PE, DVT following knee or hip replacement surgery	S
	Azilsartanmedoxomil	Hypertension	S
	Gabapentin enacarbil	Restless legs syndrome	S
2014	Ceftolozane/tazobactam	Intraabdominal infections and UTI	F, P
	Pembrolizumab	Unresectable melanoma	O, B, P, A
2015	Daclatasvir	Hepatitis-C	F, P
	Evolocumab	For high cholesterol	O
2016	Sofusbuvir; Velpatasvir	Hepatitis-C	F, B, P
2017	L-glutamine oral powder	Sickle cell disease	

P - Priority review, S - Standard review, O - Orphan designation, F- Fast track

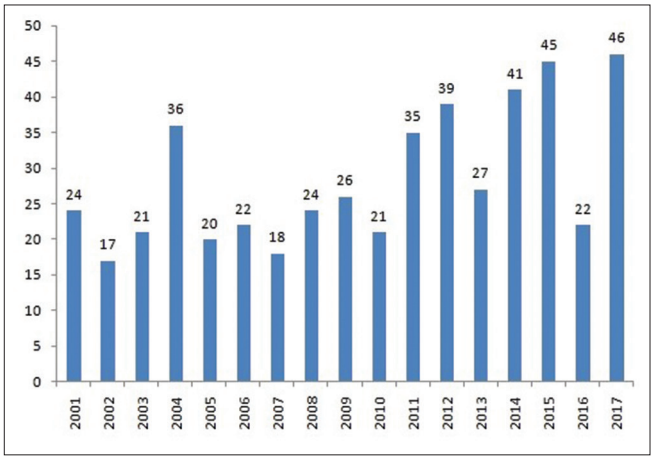

Figure 1: Year-wise new drug approvals

20 first in class approvals (agents with a unique mechanism of action) in 2012, 16 in 2015, and 15 in 2017. Those are relatively high numbers; between 1987 and 2011, FDA first in class approvals was fairly steady and ranged from roughly 3 to 15 agents per year (note that these ranges are for new molecular entities (NMEs) only, not NMEs and biologics). CDER had 18 orphan approvals in 2017, 9 in 2016, and 21 orphan approvals in 2015 as compared to 5 orphan approvals on an average from 2000 to 2010. Those are some of the highest numbers in recent years; hence, the number of FDA orphan approvals has been steadily increasing since 2000. So, the unique and new qualities of the drugs submitted to the FDA in 2017 and 2015 may have contributed to the increase in CDER approvals. Figure 2 shows number of orphan drugs approved each year.

3. Increase in first cycle approvals:

From 2011 to 2016, CDER approved 204 novel drugs, of which 166 (81%) were approved on the first cycle. In 2017, 39 of the 46 novel drugs (85%) were under "first cycle" of review.[9] The rate for 2017 is consistent with this average. This high proportion of first cycle approval reflects the extensive discussions between CDER staff and drug developers that go on during drug

Table 3: List of anticancer agents approved in last 2 decades

Anticancer agents				Review type
Year-wise	**No:**	**Drug**	**Indication**	
2000	2	Triptorelin pamoate	Advanced prostate cancer	S
		Arsenic trioxide	Acute promyelocytic leukemia	P, O
2001	1	Imatinib mesylate	CML	P, O
2002	2	Oxaliplatin	Metastatic cancer of colon or rectum	P
		Fulvestrant	Meta breast cancer	S
2003	3	Gefitinib	Meta nonsmall cell lung cancer	P
		Bortezomib	Multiple myeloma	P, O
		Abarelix	Advanced prostate cancer	P
2004	4	Pemetrexed disodium	Malignant pleural mesothelioma	P, O
		Azacitidine	Myelodysplastic syndrome and CML	P, O
		Erlotinib HCl	Nonsmall-cell lung cancer	P
		Clofarabine	Relapsed or refractory ALL	P, O
2005	2	Nelarabine	T-cell ALL	P, O
		Sorafenib tosylate	Advanced RCC	P, O
2006	4	Sunitinib malate	Gastrointestinal stromal tumor	P
		Decitabine	MDS	S, O
		Dasatinib	CML	P, O
		Vorinostat	Cutaneous T-cell lymphoma	P, O
2007	4	Lapatinib	Breast cancer	P
		Tesirolimus	RCC	P, O
		Ixabepilone	Meta breast cancer	P
		Nilotinib	CML	S, O
2008	3	Bendamustine hydrochloride	CLL	P, O
		Iobenuane	Pheochromocytoma	P, O
		Degarelix	Prostate cancer	S
2009	4	Everolimus	Advanced RCC	P
		Pralatrexate injection	Relapsed or refractory peripheral t-cell lymphoma	P, O
		Pazopanib tablet	Advanced RCC	S
		Romidepsin for infusion	Cutaneous T-cell lymphoma	S
2010	2	Cabazitaxel	Prostate cancer	P
		eribulin mesylate	Metastatic breast cancer	P
2011	6	Brentuximab vedotin	Hodgkin's lymphoma and ALCL	P, O
		Vandetanib	Meta medullary thyroid cancer	P, O
		Eribulin mesylate	metastatic breast cancer	P, O
		Crizotinib	Nonsmall cell lung caner	P, O
		Vemuranfenib	Metastatic melanoma	P, O
		Abiraterone acetate	Prostate cancer	P
2012	9	Vismodegib	Basal cell carcinoma	P
		Carfilzomib	Multiple myeloma	O, F, A
		TBO-filgrastim	Cancer chemotherapy-induced severe neutropenia	
		Enzalutamide	Prostate cancer	F, P
		Bosutinib	CML	O
		Regorafenib	Colorectal cancer	F, P
		Omacetaxine mepesuccinate	CML	O, A
		Cabozantinib	Medullary thyroid cancer	O, F, P
		Ponatinib	CML	F, O, P, A
2013	7	Pomalidomide	Multiple myeloma	O, F, A
		Ado-trastuzumab emtansine	Metastatic breast cancer	F, P
		Radium Ra 223 dichloride	Metastatic prostate cancer	F, P
		Dabrafenib	Melanoma	O, F
		Trametinib	Melanoma	O, F
		Afatinib	Metastatic nonsmall cell lung cancer	O, F, P
		Ibrutinib	Mantle cell lymphoma	O, F, B, P, A

Contd...

Table 3: Contd...

Anticancer agents				Review type
Year-wise	**No:**	**Drug**	**Indication**	
2014	4	Olaparib	Advanced ovarian cancer.	O, P A
		Idelalisib	Blood cancer	O, F, B, P, A
		Belinostat	peripheral T-cell lymphoma	O, F, P, A
		Ceritinib	Nonsmall cell lung cancer	O, B, P, A
2015	10	Alectinib	ALK-positive lung cancer	O, B, P, A
		Ixazomib	Multiple myeloma	P, O
		Osimertinib	Nonsmall cell lung cancer	P, O
		Cobimetinib	Advanced melanoma	P, O
		Trabectedin	Soft tissue sarcomas	P, O
		Trifluridine and tipiracil	Advanced colorectal cancer	S
		Sonidegib	BCC	S
		Panobinostat	Multiple myeloma	P, O
		Lenvatinib	Refractory thyroid cancer	P, O
		Palbociclib	Metastatic breast cancer	P
2016	2	Venetoclax	Lymphocytic leukemia	P, O
		Rucaparib	Ovarian cancer	P, O
2017	9	Acalabrutinib	Mantle cell lymphoma	P, O
		Abemaciclib	Metastatic breast cancers	P
		Copanlisib	Relapsed follicular lymphoma	P, O
		Enasidenib	Refractory AML	P, O
		Neratinib maleate	Reduce the risk of breast cancer returning	S
		Midostaurin	AML	P, O
		Brigatinib	(ALK)-positive nonsmall cell lung cancer	P, O
		Niraparib	recurrent epithelial ovarian, fallopian tube, peritoneal cancer	P, O
		Ribociclib	advanced breast cancer	P

P - Priority review, S - Standard review, O - Orphan designation, F- Fast track, A- Accelerated review, B- Break through review

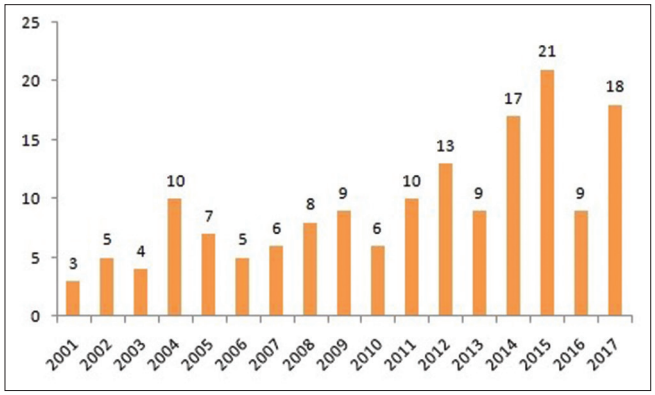

Figure 2: Number of orphan drugs approved over a period of years

development. Hence, it is important that an application contains all the relevant information which the CDER needs to know and fully review.

Current FDA Expedited Approval Programs: Additionally, the manner in which the FDA works with industry on new drug development programs has been evolving. The FDA now offers four paths for expedited development and/or review, which can be used singly or in conjunction with each other: fast track, breakthrough therapy, priority review, and accelerated approval.[10] In 2017, 18 of the 46 approved novel drugs (39%) had fast track designation namely ocrelizumab for multiple sclerosis, valbenazine for tardive dyskinesia etc.; 17 (37%) were designated as breakthrough therapies like ribociclib for breast cancer, niraparib for ovarian cancer, etc.; 28 (61%) were given priority review, e.g. dupilumab for atopic dermatitis, midostaurin for acute myeloid leukemia, etc.; and 6 (13%) received accelerated approval like benznidazole for Chagas disease. Use of these expedited programs has been steadily increasing since the year 2000.

The breakthrough therapy designation was created in 2012, so it has only recently begun to take effect. But use of the designation is increasing: there were 17 approvals in 2017 as compared to 3 approvals in 2013. In other words, expedited programs increase the speed at which new drugs are developed and reviewed, which could contribute to the number of CDER approvals in recent years. Accelerated regulatory pathways for the development of new drugs in the U.S., Europe, and Japan intend to bring novel treatments to patients more quickly. These have multiplied in the recent years, offering opportunities, benefits, and challenges for developers, patients, regulators, and payers.[11]

4. Therapeutic Area

Between 2000 and 2017, cancer therapeutics generated more fast track, accelerated, and priority approvals than any other therapeutic area.[12-14] This fact is particularly interesting because in 2015, oncology was the single largest therapeutic area for which new drugs were approved. Again there is a hike in 2017, 12 out

Table 4: List of biologics approved in last 2 decades

Biologics				Review type
Year-wise	**No:**	**Drug**	**Indication**	
2000	1	GemtuzumabOzogamicin	AML	P, O
2001	0			
2002	0			
2003	0			
2004	5	Cetuximab	Colorectal cancer	P
		Bevacizumab	Metastatic cancer of the colon and rectum	P
		Technetium 99m Tc scintigraphicimagingFanolesomab	Scintigraphic imaging	S
		Natalizumab	Multiple sclerosis	P
		Palifermin	Hematologic malignancies	P
2005	2	Galsulfase	Mucopolysaccharidosis VI	P, O
		Abatacept	RA	P
2006	4	Alglucosidase alfa	Pompe disease	P, O
		Ranibizumab	Neovascular (wet) ARMD	P
		Idursulfase	Mucopolysaccharidosis II	P, O
		Panitumumab	EGFR-expressing meta colorectal cancer	P
2007	1	Eculizumab	PNH	P, O
2008	2	Rilonacept	CAPS	P, O
		Certolizumab pegol	Crohn's disease	S
2009	4	Golimumab	RA, psoriatic arthritis	S
		Canakinumab	Cryopyrin-associated periodic syndrome	P, O
		Ustekinumab	Psoriasis	S
		Ofatumumab	CLL	P, O
2010	2	Denosumab to	Osteoporosis in postmenopausal women	S
		tocilizumab	Severe RA	S
2011	3	Belimumab	Autoantibody-positive lupus	P
		Ipilimumab	Metastatic melanoma	P, O
		Belatacept	Prevent organ rejection	S, O
2012	3	Pertuzumab	metastatic breast cancer	P
		Ziv-aflibercept	Colorectal cancer	P
		Raxibacumab	Inhalational anthrax	O, F, P
2013	1	Obinutuzumab	CLL	O, B, P
2014	7	Blinatumomab	B-cell ALL	O, B, P, A
		Nivolumab	Metastatic melanoma	O, F, B, P, A
		Pembrolizumab	Unresectable melanoma	O, B, P, A
		Peginterferon beta-1a	Multiple sclerosis	
		Vedolizumab	Ulcerative colitis and Cr D	F, P
		Siltuximab	Castleman's disease	O, P
		Ramucirumab	Stomach cancer	O, F, P
2015	9	Elotuzumab	Multiple myeloma	O, P, B
		Necitumumab	squamous non-small cell lung cancer	O, F
		Daratumumab	Multiple myeloma	O, F, B, P, A
		Mepolizumab	Asthma	
		Idarucizumab	Reverse dabigatran's effects	O, B, P, A
		Evolocumab	High cholesterol	O
		Alirocumab	High cholesterol	
		Dinutuximab	Neuroblastoma	O, P
		Secukinumab	Plaque psoriasis	S
2016	7	Obiltoxaximab	Inhalational anthrax	S, O
		Ixekizumab	Moderate-to-severe plaque psoriasis	S
		Reslizumab	Severe asthma	S
		Atezolizumab	Urothelial carcinoma,	P
		Daclizumab	Multiple sclerosis	S
		Olaratumab	Soft tissue sarcoma	P, O
		Bezlotoxumab	Clostridium difficile infection	P

Contd...

Table 4: Contd...

		Biologics		Review type
Year-wise	**No:**	**Drug**	**Indication**	
2017	11	Emicizumab	bleeding episodes in patients with hemophilia A	P, O
		Vestronidase alfa	mucopolysaccharidosis type VII (MPS VII)	P, O
		Benralizumab	asthma with an eosinophilic phenotype	S
		Inotuzumabozogamicin	Refractory ALL	P, O
		Guselkumab	Mod to severe plaque psoriasis	P
		Sarilumab	RA	S
		Durvalumab	Metastatic urothelial cancer	P
		Ocrelizumab	Multiple sclerosis	P
		Dupilumab	atopic dermatitis	P
		Avelumab	Merkel cell cancer	P, O
		Brodalumab	Moderate-to-severe plaque psoriasis	S

P - Priority review, S - Standard review, O - Orphan designation, F- Fast track, A- Accelerated review, B- Break through review

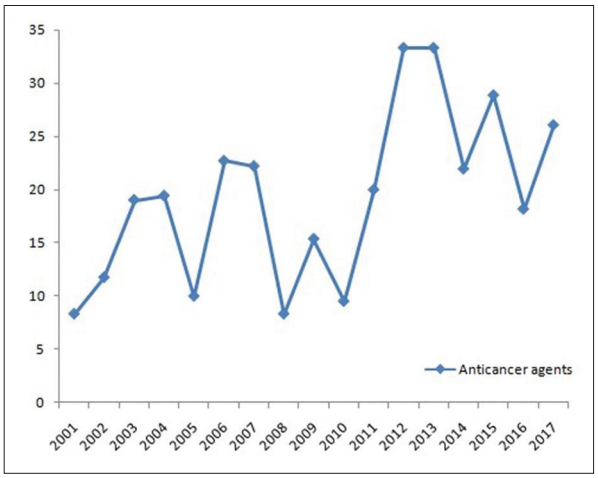

Figure 3: Trend in anticancer drug approval over a period of years

of 46 drugs are anticancer agents. Perhaps in 2018, 23 out of 55 are anticancer drugs.[5] The constant need for cancer therapeutics, coupled with their proven track record for obtaining accelerated approval (based on surrogate endpoints), may have contributed to their approval rate in recent years. Table 3 highlights list of approved anticancer drugs. Figure 3 depicts trend of the same.

Various categories in drug approval process are as follows:

First-in-class

A drug with, first of its kind mechanism of action and totally different from already available set of drugs for a medical condition belongs to first in Class drug approval process. Some notable approvals in this category include ocrelizumab for multiple sclerosis (2017), palbociclib (2015) for metastatic breast cancer, etc.

Drugs for rare diseases (orphan drugs)

Drugs approved for a small population of patients, i.e. less than 200,000 people are known as orphan drugs. Rare disease patients have very limited options for their treatment. Examples of orphan drugs are mentioned in Tables 1, 3, and 4.

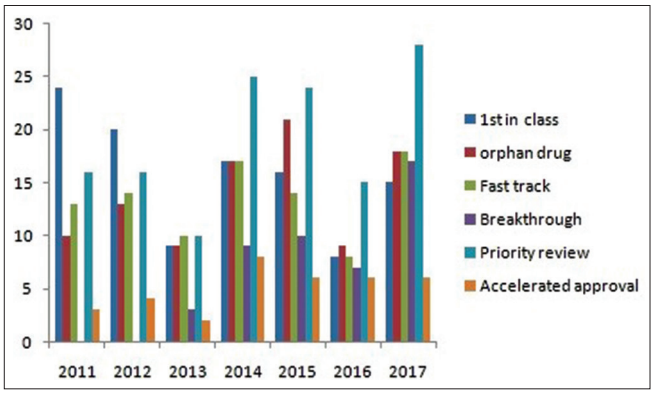

Figure 4: Drug designation summary overview from 2011 to 2017

First cycle approval

Drug approval process which consists of only one cycle of review belongs to this category. Maximum numbers of drugs get approval under this designation, e.g. Deflazacort (2017) for Duchenne muscular dystrophy, evolocumab (2015) for hypercholesteremia.

Combined expedited approval methods: CDER applies innovative regulatory approval methods like fast track, accelerated approval, priority review, breakthrough approval and expanded access programs [Table 6].[10,15] Many times, NMEs require more than one drug approval process from the above-mentioned categories. These help in expediting timelines from research and development to availability in the market. Examples of drugs approved under more than one category are mentioned in Tables 3, 4, and 5. Figure 4 gives an overview of drug designation summary from 2011 to 2017. In March 2017, the US FDA has also introduced the new Regenerative Medicine Advanced Therapy (RMAT) which is a new program to facilitate and expedite development and review of regenerative medicines.[16]

Discussion

CDER and pharmaceutical industry work together in bringing innovation in research and development of new drugs. Starting

Table 5: List of antiviral agents approved in last 2 decades

Year	No:	Antiviral agents Drug	Indication	Review type
2000	1	Lopinavir, ritonavir	HIV-1	P
2001	1	Tenofovir disoproxil fumarate	HIV-1	P
2002	1	Adefovir dipivoxil	Ch Hep B	P
2003	3	Enfuvirtide	HIV-1	P
		Atazanavir	HIV-1	P
		Emtricitabine	HIV-1	S
2004	0			
2005	2	Tipranavir	HIV-1	P
		Entecavir	Ch Hep B	P
2006	2	Darunavir	HIV	P
		Telbivudine	Chr Hep B	S
2007	2	Maraviroc	HIV-1	P
		Raltegravir potassium	HIV-1	P
2008	1	Etravirine	HIV-1	P
2009	0			
2010	0			
2011	3	Rilpivirine	HIV-1	S
		Telaprevir	HCV	P
		Boceprevir	HCV	P
2012	1	Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil, fumarate	HIV-1	F
2013	3	Dolutegravir	HIV-1	F, P
		HCV	Simeprevir	F, P
		HCV	Sofosbuvir	F, B, P
2014	3	Ledipasvir/sofosbuvir	HCV	F, B, P
		Ombitasvir, paritaprevir, and ritonavir tablets copackaged with dasabuvir tablets	HCV	F, B, P
		Peramivir	influenza infection	F
2015	2	A fixed-dose combination tablet containing elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide	HIV-1	S
		Daclatasvir	HCV	P
2016	2	Elbasvir; grazoprevir	HCV	P
		sofosbuvir; velpatasvir	HCV	P
2017	2	Glecaprevir and pibrentasvir	Ch HCV	P
		Sofosbuvir, velpatasvir and voxilaprevir	Ch HCV	P

P - Priority review, S - Standard review, O - Orphan designation, F- Fast track, A- Accelerated review, B- Break through review

Table 6: Expedited drug approval methods

Fast track approval
Drugs with the potential to address unmet medical needs. Fast track speeds new drug development and review, either by increasing the level of communication to drug developers or reviewing portions of a drug application ahead of the submission of the complete application
Breakthrough approval
Drugs with preliminary clinical evidence demonstrating that it may result in substantial improvement on at least one clinically significant endpoint (i.e., study result) over other available therapies for serious conditions. A breakthrough therapy designation includes all of the fast track program features, as well as more intensive FDA guidance on an efficient drug development program. Shorten the development time of a potential new therapy
Priority review
Drug could potentially provide a significant advance in medical care and set a target to review the drug within six months instead of the standard 10 months.
Accelerated approval
Early approval of a drug for a serious or life-threatening illness that offers a benefit over current treatments based on a "surrogate endpoint" (e.g., a laboratory measure) or other clinical measure that is considered reasonably likely to predict a clinical benefit of the drug. But, after approval, the drug must undergo additional testing to confirm that benefit. (Phase-IV)

from testing and manufacturing process to understanding of science of the disease, FDA provides complete guidance through CDER.

CDER plays a crucial role in bringing innovation to drug development process approving new drugs and biological products. These include both new class of drug or drugs belonging to same class with few addition or deletions in the molecular structure.[17] FDA approval of a new drug is extremely challenging. Rate of drug approval is much higher than previous years. We also observed that medical needs and disease pattern are usually not changing drastically but knowledge from basic research and unmet medical needs are likely to provide market for pharmaceuticals. Right to Try Act, 2017 may compromise patient's safety in a hurry by giving access to new drugs.[18]

Since the year 2000, there has been a steady rate of introduction of new drugs by CDER, out of which expedited approval of anticancer and biologics is seen as recent trend in drug development. But stringent norms have been followed in this process, i.e. without compromising the safety and quality which has indeed led to efficacious drugs coming up in the market. On the contrary, slow progress in approval of antiviral drugs especially anti HIV/Hepatitis C virus (HCV) and lifestyle diseases was seen. A total of 59 novel molecules have been approved in 2018. Also, in 2019, due to expedited drug approval programs, trends are likely to remain the same. Is it because of change in prevalence of disease pattern or market-driven profitability? There is a need to conduct studies to get some insight into changing trends in approvals over last 2 decades by FDA.

This trend in drug approvals by U.S. Food and Drug Administration (USFDA) sooner or later will come in India as well, since there are no innovations from our side. However, considering the disease burden of our nation, which mostly comprises of infectious diseases like tuberculosis, malaria apart from cancer, diabetes, hypertension: novel agents being approved by USFDA every year do not suffice the unmet need of our country.

Nowadays, primary care is increasingly being promoted, by government sector and health funders worldwide, as the preferred setting for most health care for various reasons, such as increasing need, to stabilize health-care costs, and to accommodate patient's preference for care close to home.[19] So, it is prudent that primary care physicians should be well versed with new drug approval and its clinical applications. At the same time, it is difficult for them to keep track on such large number of drugs being approved by the USFDA every year. But among these drugs, certain drugs have clear cut indications in primary care like eluxadoline use in diarrhea-predominant IBS, lesinurad in combination with a xanthine oxidase inhibitor for the treating hyperuricemia associated with gout.[20]

Primary care physicians also get to learn from peers which has been reflected in their clinical practice by prescribing some novel agents like dabigatran, sitagliptin, and aliskiren in the past.[21] Nowadays, after getting diagnosed with cancer and autoimmune diseases many patients are going to primary care centers for follow-ups or remaining infusions. So, it is a must for physicians working in primary care set ups to be updated with recent drug approvals and new indications of the already approved drugs.

Limitations

We were unable to analyze extent of rejections of new drug applications due to lack of access to FDA data. Also, quality of documentation and its clinical impact over last two decades could not be studied.

Conclusion

We found there has been a steady rate of introduction of new drugs by CDER over the last 2 decades. Expedited approval of anticancer and biologics is seen as recent trend in drug development providing access to investigational medicines. Relatively, slow progress in approval of drugs for neurological disorders (depression, psychosis, multiple sclerosis, etc.) and lifestyle diseases like obesity, atherosclerosis, diabetes, etc., was seen. These findings reflect more emphasis being laid down in research for anticancer drugs and biologics. Our results suggest that FDA's existing stringent but realistic and need based system of drug approvals being followed by FDA are a big step in speedy drug development. In order to give boost to the research and development of novel molecules or drugs which can provide significant improvement over already existing ones, FDA should adopt new approaches which will give encouragement to the industry.

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Conflicts of interest

There are no conflicts of interest.

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