Original Article

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

Angelika Batta[1], Bhupinder Singh Kalra[1], Raj Khirasaria[2]

[1]Department of Pharmacology, Maulana Azad Medical College, [2]Medical Affairs, Sanofi Genzyme India, Saket District Center, Saket, New Delhi, India

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,

Address for correspondence: Dr. Bhupinder Singh Kalra, Department of Pharmacology, Maulana Azad Medical College, Bahadur Shah Zafar Marg, New Delhi - 110 002, India.
E-mail: drbskalra@gmail.com

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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

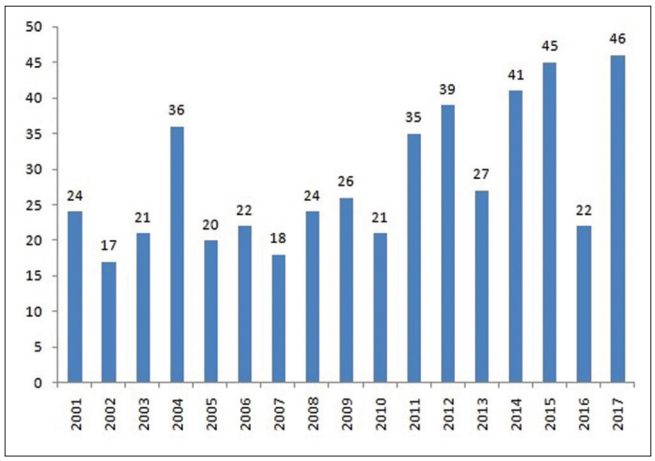

Figure 1: Year-wise new drug approvals

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

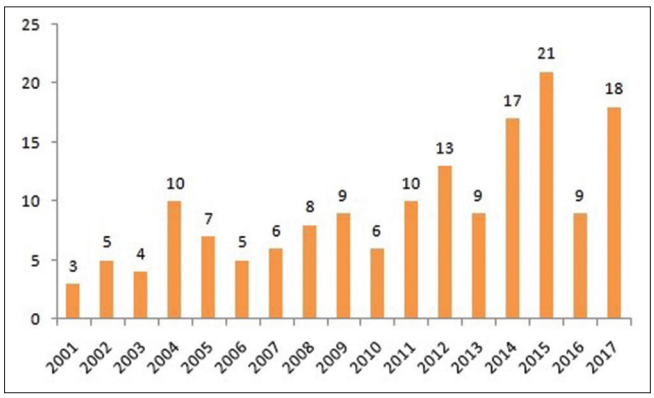

Figure 2: Number of orphan drugs approved over a period of years

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

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