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Review Article

Contemporary Drugs and Biologics with Special Significance

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ABSTRACT

Expanding science and arrival of rapid screeing of methods expedited drug discovery process. Number of molecules approved by United States –Food and Drug Administrative agency is on rise. Some drugs have been proven beneficial and some of them received gruesome post marketing experience and added controversies. This article provides comprehensive review of all such drugs that are approved between 2011 and 2015.

Key words: Newer drugs, New drug formulations, Expedited drug review, First of its kind drugs.

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INTRODUCTION

The last five years seems to be thumping success for world leading pharmaceuticals; many drugs approved by United States, Food and Drug Administrative agency (US-FDA) and thence worldwide. FDA claims many novel drugs have been approved with expedited review schemes and thereby reducing the time of available of drugs meant for 'Unmet' medical need is addressed. There are quite number of interesting drugs approved for rare or serious diseases and untreatable conditions. They are grouped under either as fast rack designation, priority review, first in class treatment, breakthrough therapy etc. About 177 molecules are approved between 2011 and 2015 and FDA announced review timeline reduced significantly from 18 months to 9 months to make the molecules available as early as possible for general public. This article provides comprehensive review of some of the significant molecules.[1]

Key words : Breakthrough therapy ,expedited review, fast track review, first in class drugs, novel drugs, newer biologics,

'First of its kind' -Drugs

Cystic Fibrosis is the most common childhood fatal genetic disease in United States. More than a decade Vertex Pharmaceutical involved in the development drugs for cystic fibrosisand achieved its goal in July 2015.

Fixed dose combination (FDC) of Ivacaftor/Lumacaftor for cystic fibrosis Though Ivacaftor was approved earlier, combination of ivacaftor/lumacaftor is the first FDC approved for this condition. This is also first personalized medicine FDC approved cystic fibrosis CFTR gene F*508del* mutation. This FDC works better than ivacaftor alone, reduces complications of cystic fibrosis and increases patient survival. Despite the significant adverse effects like hepatotoxicity FDA approved this FDC as benefits outweigh the risks involved.

Taliglucerase, a drug approved rare metabolic disorder Gauchers disease. It is effective in type I Gaucher's disease due to glucocerebrocidase deficiency and accumulation fatty foam cells in liver, spleen and other vital organs. Though it is rare disorder, it is highly mortal to patients and taliglucerase is a undoubtedly significant molecule and it is still under long term benefit evaluation by FDA. Elosulfase alfa, a remarkable molecule approved for enzyme replacement therapy for Morquio A syndrome [Mucopolysaccharidosis Type IVA [MPS IVA] by a deficiency of lyzosomal enzyme N-acetylgalactosamine-6-sulfate sulfatase.

Ruconest is the first recombinant C1 esterase inhibitor and it is one of the latest drug obtained from genetically modified rabbits, transgenic rabbit milk product. Hereditary angioedema is an untreatable condition till 2014. Drugs like androgens to inhibit C1 esterase are minimally effective. Bradykinin antagonist Icatibant failed to show significant relief. Ruconest, a signature molecule will be saving thousands of hereditary angioedema patients. When compared with other animal products, allergy and hypersentivity are less with ruconest. Adverse effects profile includes only moderate headache, nausea.

Raxibacumab, is the FDA approved drug without any human trials. It is a monoclonal antibody given against Bacillus anthracis causing inhalational anthrax. FDA considering the threat of bioterrorism approved this molecule based on animal efficacy rule under fast track designation and under orphan drug status. Obiltoxaximab is the second molecule belonging to same category approved based on efficacy in animal studies.

Talimogene laherparepvec , the first oncolytic viral treatment approved by FDA. Viruses can induce cancer , however the property of virus to induce cell response and to induce cell arrest and apoptosis induction is under evaluation since 1960.Over the span of five decades, the first oncolytic virus which is nothing but genome modified herpes virus approved for melanoma. Approval was based on efficacy showing decrease in tumor size of abot 430patients at various sites who are having advanced non resectable melanoma skin cancer. Being a live herpes virus, chance of activation of virus in the body cannot be obviated.

Belimumab, the first biologic approved systemic lupus erythematosus (SLE). Among auto immune disorder, SLE is the common cause of significant morbidity and mortality. It is multisystem disorder affecting kideney (*Lupus nephitis*), spleen, marrow, joints, central nervous system etc. Immunosuppressant's remains the constant treatment for SLE and arrival of B cell activator inhibitor, Belimumab is expected to produce greater benefits for SLE patients.

Centruroides immune fab is the first specific drug approved FDA as envenomation for scorpion stings. This is significant approval based on only fifteen number of trial involving children with severe symptoms of scorpion sting. This molecule approved as orphan drug and on continuing evaluation for its safety and efficacy

Telaprevir and bociprevir, non-retro viral protease inhibitors are first specific anti Hepatitis C drug. Hepatitis C is still the most common hepatitis untreatable condition causing thousands of patients liver cirrhosis, hepatocellular carcinoma and death. Arrival of these drugs considered as a boon for hepatitis C harbouring patients.

Trabectedin is a tetrahydroisoquinoline molecule. It is the first class of anticancer drug having unique mechanism of action affecting gene

transcription regulator factor. It is effective in rare aggressive leiomyosarcoma tumor. It is approved based on its efficacy to increase survival of unresectable surgical sarcoma. Trabectedin is prone to cause cardimyopathy and rhabdomyolysis.

Alirocumab and evocolomumab, is a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor used for reduce severe hypercholesterolemia seen in heterozygous familial hypercholesterolemia. These novel hypolipidemics are given once in two weeks injection, just like mipomersen which is a recently approved another novel antisense oligolucelotide molecule given as once weekly hypolidemic injection. PSCK9 inhibitos acts b destabilising Low density cholesterol in peripheral cells and there by facilitates their hepatic uptake.

Gadobuorol, is the first FDA approved contrast that can be given for children under 2 years of age. Bella fill is dermal filler used for cosmetic correction of facial nasolabial folds. Uridine triacetate, the new chemoprotectant for flurouracil and capecitabine toxicity. infliximab-dyyb, the first bio similar anti tumour necrosis factor for autoimmune diseases, ospemifene for primary dyspareunia, sebelipase alfa for lysosomal acid lipase deficient disorder, sugammadex as a neuromuscular selective relaxant binding agent against vecuronium and rocuronium, asosulfatase alfa for hypophosphotasia, ruxolotinib and tofocitinib, janus kinase inhibitors for rheumatic arthritis are the other breakthrough therapies emerged in recent years whereas ruxolotinib is already approved for primary myelofibrosis

Apart from novel mechanism, certain conventional drugs approved for different routes of administration. Significant to mention are nasal naloxone for opoid overdose, inhalational insulin afreeza, N-acetylcysteine effervescent tablet for paracetamol overdose instead of intravenous injection, sumatriptan auto injector for migraine, chewable methyphendilate for attention deficit hyperactivity disorder, bruprenorphine and fenatanyl buccal film for chronic pain and inhalational glycopyrolate for chronic asthma and chronic obstructive pulmonary disease.[2-5]

Significant molecules fulfilling unmet medical need

Abiraterone, 17-alpha hydroxlase inhibitor, reduces synthesis of testosterone and its by-products. Androgens promote the survival prostate cancer which is one the most commonly diagnosed cancer among males and prognosis is bad even in early stages. Some of the advanced metastatic cancer that are treated with complete blockade of androgen with androgen receptor blockers also has ability to progress and known as' Castration resistant metastatic prostate cancer'. Abiraterone, being testosterone synthesis inhibitor has shown improvement in last stages of prostate cancer patients when given with corticosteroids. This drug was approved under fast track designation after evaluation from one clinical trial finding involving 1195 patients. The end point considered was increase in survival of 4.5 months compared to standard treatment.

Vemurafenib, a molecule can be categorised under personalized medicine. It is approved for last stage melanoma. Melanoma, by itself carries worst prognosis among all skin malignancy and highly fatal. Dacarbazine, an alkylating used to treat melanoma was used against vemurafenib as a comparator. Vemurafenib has been shown effective against melanoma subtype patients with BRAF V600 mutation. Vemurafenib was evaluated under expedited programme and approved despite its propensity to induce sqauamaus carcinoma in survivors.

Brentuximab vedotin, Anti CD-30another fast track molecule approved just after one clinical trial conducted with 107 anaplastic large cell lymphoma. It is one of the very rare type lymphoma with no convincing treatment. Brentuximab is not devoid of adverse effects, it can produce neuropathy and myelosuppression. Average time from application to approval was less than six months by FDA. Similarly, Bruton's tyrosine kinase inhibitor(BTK inhibitor) ibrutinib was approved for fatal mantle cell lymphoma in 2013 is also claimed to be fulfil the unmet need for rare lymphoid cancers.

Methotrexate, a conventional anticancer antimetobolite used in osteosarcoma and remain as drug of choice in choriocarcinoma. Methotrexate, high dose regime with Leukovorin (HDM-L) is employed to reduce its adverse effects. However the active form folinic acid is incapable when methotrexate reaches its peak level in patients with low body surface area and succumb them to severe toxicity. Glucapdiase, a caboxypeptidase function as methotrexate cleaving agent and reduces its serum concentration rapidly and thereby prevents toxicity rapidly. Glucarpidase was granted expedited drug review process as well as designated orphan drug status.

The classical four generations of cephalosporin's stepped into fifth generation with a molecule ceftaroline. In the era bacterial resistance and emergence of 'superbug', the synthesis of antibiotics is becoming very less. US FDA promotes synthesis of antibiotics under GAIN act , Generating antibiotics incentives act. Ceftaroline is effective methicilln resistant staphylococcus infections in skin and pneumonia.

Dalbavancin and Oritavancin, new glycopeptide call wall inhibitors and newer congener of Linezolid , namely Tedizolid which inhibits protein synthesis approved in 2014 by US FDA to treat complicated acute bacterial skin and skin associated infections by virulent organisms including Vancomycin resistant staphylococcus.

Cardiac failure remains the most common morbidity and mortality affecting global population. Shift of treatment approach from symptomatic relief to retard the progression of heart failure is supported by angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers(ARB), aldosterone antagonist and cardioselective betablockers. Discovery and combination Nepriylsin inhibitor with ACE inhibitor was associated with severe angioedema. The drawback associated with this combination is succeeded by combination of Neprylsin inhibitor, Sacubutril with angiotensin receptor blocker valsartan(ANRI). This approval based as PARADIGM-HF mutli centric trial by Novartis. Superior efficacy of this combination is to be evaluated over long term.

Bedaquiline, an Indian product discovered specifically for Tuberculosis after forty years of having first line TB drugs. It is an ATP synthase inhibitor, showing positive improvement even in cases of multi drug resistant tuberculosis (MDR-TB). It is approved by FDA and Central drug standard control organisation (CDSCO), India in selective regions with high prevalence of MDR- TB. Similarly, Miltefosine is approved for leishmanisis and it is the first oral drug for leishmaniasis developed in India and started using in North eastern states with high prevalence of Leishmaniasis. Mechanism of action of miltefosine is not clearly understood, it appears to interact with cell phosphoplipid of parasite and causes apoptosis.[2-6]

Drug associated controversies

Flibanserin, colloquially called as female Viagra, is a serotonin analogue granted approval by FDA for hypoactive sexual desire disorder of women. FDA disapproved this molecule twice due to lack of data on efficacy. Sprout pharmaceuticals cleverly convinced women communities of United States to initiate chaos, why female should not enjoy the benefits of flibanserin when males are allowed to use sildenafil. Under legal judgement FDA took review flibanserin third time and granted approval with caution stating its propensity to cause sedation, light headedness.[7]

Dabigatran, after several decades an oral anticoagulant as an alternative to warfarin was developed by *boehringer ingelheim* pharmaceuticals. Warfarin associated with adverse effects and drug interactions, mandates very precise dose administration and monitoring. Dabigatran, first oral direct thrombin inhibitor was claimed to reduces thromoboembolic episodes and to possess less bleeding tendency. However, dabigatran

Table 1: Drugs approved with 'first of its kind' category

Drug/Biologics	Category	Indication
Ivacaftor/Lumacaftor	First FDC targeted CFTRF *508del* mutation	Cystic fibrosis
Ruconest	First recombinant C1 esterase inhibitor from milk of transgenic rabbit	Hereditary angioedema
Raxibacumab	First drug approved based animal efficacy studies only	Inhalational anthrax
Talimogene laherparepvec ,	First oncolytic viral treatment	Melanoma
Belimumab	First biologic for systemic lupus erythematosus	Systemic lupus erythematosus
Telaprevir	First non retro viral protease inhibitor	Hepatitis C
Mipomersen	First antisense oligonucleotide against cholesterol molecule	Hereditary hypercholesterolemia
Evolocumab	First biologic against cholesterol	Hereditary hypercholesterolemia
Centruroides immune fab	First approved immunotoxin for scorpion sting	Neurotoxic scorpion sting
Trabacetedin	First transcription factor regulator	Firbosarcoma
Gadobuorol	First contrast to be used in kids below 2 years	MRI imaging
Infliximab dybb	First bio similar anti TNF	For Chron's disease, Rheumatoid arthritis etc
Uridine triacetate	First chemoprotectant for pyrimidine analogues	Fluorouracil and capecitabine overdose
Ospemifene	Serotonin analuge	Primary dyspareunia
Ruxolotinib,	First Janus kinase inhibitor	Primary myelofibrosis
Sugammadex	Neuromuscular selective relaxant binding agent	To reverse vecuronium and rocuronium induced muscle relaxation ,
Sebelipase alfa	First recombinant enzyme for Lysosomal acid lipase	Lysosomal acid lipase deficient disorder,
Asosulfatase alfa	First Recombinant asosulfatase	Hereditary hypophosphatasia
Taliglucerase,	First recombinant enzyme for Glucocerbrocidase	Type I Gaucher's disease
Elosulfase alfa	First lyzosomal enzyme N-acetylgalactosamine-6-sulfate sulfatase.	Morquio A syndrome

Table 2: Drugs approved with new dosage forms

Drug	New dosage from	Indication
Buprenorphine	Bucaal film	Chronic pain
Fentanyl	Buccal film	Chronic pain
Nalaxone	Nasal spray	Opioid overdose
Acetylcysteine	Effervescent tablet	Paracetamol poisoning
Methyphedilate	Chewable tablet	Attention deficit hyperactivity disorder
Sumatriptan	Auto injector	Migraine
Afrezaa	Inhalational insulin	Diabetes mellitus
Glycopyrollate	Inhalational spray	Chronic obstructive pulmonary disease

Table 3: Newly approved drugs and biologics towards unmet medical need

Drug/Biologics	Category	Indication
Abiraterone	Testosterone synthesis inhibitor	Metastatic castration resistant prostate cancer
Vemurafenib	BRAF V600 inhibitor	Non reseactable advanced melanoma
Brenutiximab	Anti CD 30	Large anaplastic lymphoma
Glucarpidase	Carboxipeptidase	Methotrexate toxicity
Ceftaroline	First generation cephalosporin	Skin infections by methicillin resistant staphylococcus
Sacubutril	Nepriylsyn angiotensin receptor blocker	Congestive cardiac failure
Bedaquiline	ATP synthase inhibitor	Multidrug resistant tuberculosis
Miltefosine	Cell wall phospholipid disruption	Leishmaniasis
Dalbavancin, Oritavancin	Glycopeptides	Vancomycin resistant staphylococcus
Tedizolid	*Oxazolidinone*	Vancomycin resistant staphylococcus and enterococci infections

Table 4: Newly approved drugs and biologics with controversies involved for against their use/approval

Drug/Biologics	Category	Indication	Controversial Element
Flibanserin	Serotonin analogue	Hypoactive sexual desire disorder of women	Approved after widespread protest by women.
Dabigatran	Oral direct thrombin inhibitor	Prophylaxis for thromboembolism	Severe bleeding episodes: mandates approval of its reversal , Idarucizumab
Simeprevir Paritaprevir	Protease inhibitor	Hepatitis C	Severe hepatic failure within few weeks of treatment
Z Mapp	Monoclonoal antibody	Proposed against Ebola viral infection	Used without proof of concept trials

associated bleeding is high and its bleeding is arrested by idarucizumab. Fast track review of dabigatran escalated the controversies involved with quality of drug review process of FDA. Idarucizumab, a monoclonal antibody developed by same pharmaceutical used to stop dabigatran induced bleeding arises of question of validity and authenticity of FDA expedited review process.[8]

Simprevir, paripatevir are the other molecules approved for hepatitis C recently associated with severe fatal hepatic injury. The mean number of days between drug intake and occurrence serious liver injury is less than forty five days. When already telaprevir and biceprevir approved for Hepatitis C, rationale for expedited review of these drugs is controversial as unexpedited standard review could have predicted toxicity which occurs within few weeks of administration.[9]

Z mapp, monoclonoal antibody though not approved it is used for two American doctors contracted ebola infection in guinea. Worldwide protest developed why such experimental molecules were used without ethical approval only for those two American doctors but not for other Ebola affected patients in African continent. Problem was resolved when Centre for disease control president, US said these molecules were given as compassionate use. This product is funded by US government and at present it is not made available for all the African ebola infected patients as more number of clinical evidence needed for global marketing.[10]

CONCLUSION

Though several molecules approved under priority basis and grated approval based surrogate marker effects, these molecules often receiving dug alert signal and even boxed warning. Some of the molecules failed to show clinical benefits as expected during evaluation.[11-12] Extensive and extended post marketing evaluation will decide fate of these molecules as well as standards of expedited drug review process.

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