Does Priority Review Result in a Higher Frequency of Drug Withdrawals From the Market Than Standard Review

by

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Abstract

Drug withdrawals happen when the FDA requests a pharmaceutical company to remove a drug from market as the risks caused by the drug outweigh the benefits. Drug withdrawals not only affect the patients but also the drug companies. The average time for a new compound to come into the market is about 12 years. The amount of resources used is also tremendously high. The main purpose of this research was to examine the drugs approved through priority review and whether they resulted in a higher frequency of drug withdrawals than standard review drugs. This analysis would also help in understanding if shorter review of drugs could help in more number of medications to reach the patient population and save lives. This research examined the number of drugs approved in the years 1992-2010 that have been withdrawn from the market. The approval process for those drugs, i.e. priority review or standard review, was available from the FDA. Twenty drugs were withdrawn from the market in this time period. Six of these drugs were approved as a priority review and 14 drugs were approved as a standard review. There is no statistical difference between the rate of withdrawal for drugs approved under priority review compared to standard review.

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Introduction

Drug development is a complex process. It takes an average of 12 years for an experimental compound to reach a patient as an approved drug. There is a 1 in 5,000 chance for a new drug to actually make it to the market. There is a lot of time and resources that are involved in this process (Drug Approvals - From Invention to Market ... A 12- Year Trip, 1999).

PDUFA (the Prescription Drug User Fee Act) was approved by Congress in 1992. PDUFA requires pharmaceutical companies to pay application fees for each New Drug Application (NDA) submitted to the FDA. This act was introduced as a result of dissatisfaction by consumers and the pharmaceutical industry with the length of the drug review process (Thaul, The Prescription Drug User Fee Act (PDUFA): Background and Issues for PDUFA IV Reauthorization, 2008).

In 1992 FDA agreed to specific PDUFA goals for improving the drug review time and created a two-tiered system of review times, Standard Review and Priority Review. A Priority Review designation means FDA's goal is to take action on an application within 6 months (Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review, 2013).

Despite careful evaluation of the drug during the review process, there are still drugs that have been and are being removed from the market due to unforeseen safety issues. According to Lasser et al. (2002), nearly 20 million people in the US took at least 1 of the 5 drugs withdrawn from September 1997to September 1998. Seven drugs approved since 1993 lead to the death of approximately 1000 patients (Lasser et al. 2002). These drugs included Cisapride which led to the death of 24 infants (Lasser et al. 2002).

Regulation of Approved Drugs by FDA

FDA regulates the drugs that have been introduced into the market mainly through Center for Drug Evaluation and Research (Thaul, How FDA Approves Drugs and Regulates Their Safety and Effectiveness, 2012). The Office of Surveillance and Epidemiology (OSE) is the primary group that is responsible for Drug Post Approval Regulation (Thaul, How FDA Approves Drugs and Regulates Their Safety and Effectiveness, 2012).

FDA regulates drug safety through various means (Thaul, How FDA Approves Drugs and Regulates Their Safety and Effectiveness, 2012). The MedWatch program was established to monitor adverse events. Public and physicians use MedWatch to report adverse events. This process allows FDA to monitor the drug after it is released to the market. The FDA also reviews studies conducted by manufacturers. It requests labelling changes when the drug shows new adverse effects. The agency also monitors published literature that has information about marketed drugs. It remains in contact with other international regulatory bodies such as the EMEA and Health Canada.

FDA may request additional Phase 4 Trials for drugs to monitor the long term effects of a drug. Pharmacovigilance tools include MedWatch and the Adverse Event Reporting Systems (AERS) for monitoring approved drugs. Drug companies report all the adverse events to the FDA. If the drug companies fail to do the FDA issues Warning letters. Regulatory action can be can be taken by the FDA if the manufacturing company of the drug does not take any action even after FDA asked them to voluntarily withdraw the drugs. Despite efforts from the FDA to improve the drug approval process, some of drugs are still withdrawn from the market. There is a desire to reduce the number of drug withdrawals from the market (Ahmad, 2003).

Background

According to Qureshi et al. (2011), there were 740 NMEs approved from the years 1980-2009, out of which 22% of the drugs were withdrawn from the market due to safety reasons.

Figure 1. shows the number of approvals and percentage of drug withdrawals due to safety reasons of NMEs from 1981-2010 on a 5 year cohort bases

Figure 1. Safety Based NME Withdrawal Percentages from 1980-2010

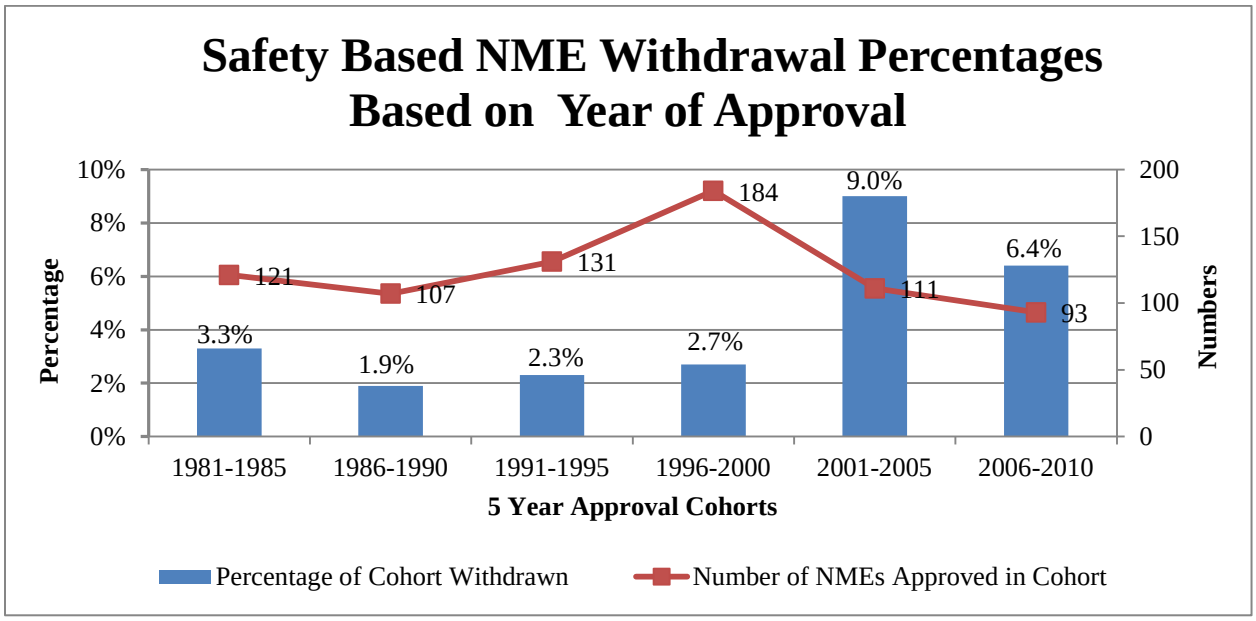

Figure 1: Data is updated from the table from the report "Centre for Drug Evaluation and Research. Report to Nation. Improving Public Health through Human drugs." from http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM079006.pdf

The number of drugs that were withdrawn from the market was 3.3% during 1981-1985 and 1.9%. After the PDUFA began, the number of drug withdrawals were 2.3% and 2.7% for 1991-1995 and 2.7% for 1996-2000. For the cohorts 2001-2005 and 2006-2010 the withdrawal increased to 9% and 6.4% of the approved drugs (Dagumalli & Martin, 2012).

The rates of safety-based market withdrawals of NMES did not change before PDUFA and after PDUFA has been introduced (FDA, 2007). Figure 2 shows that the rates of safety based withdrawals of NMEs are similar before and after user fees has been collected.

Figure 2. Safety Based Withdrawals from 1971-1992 and 1992-2007

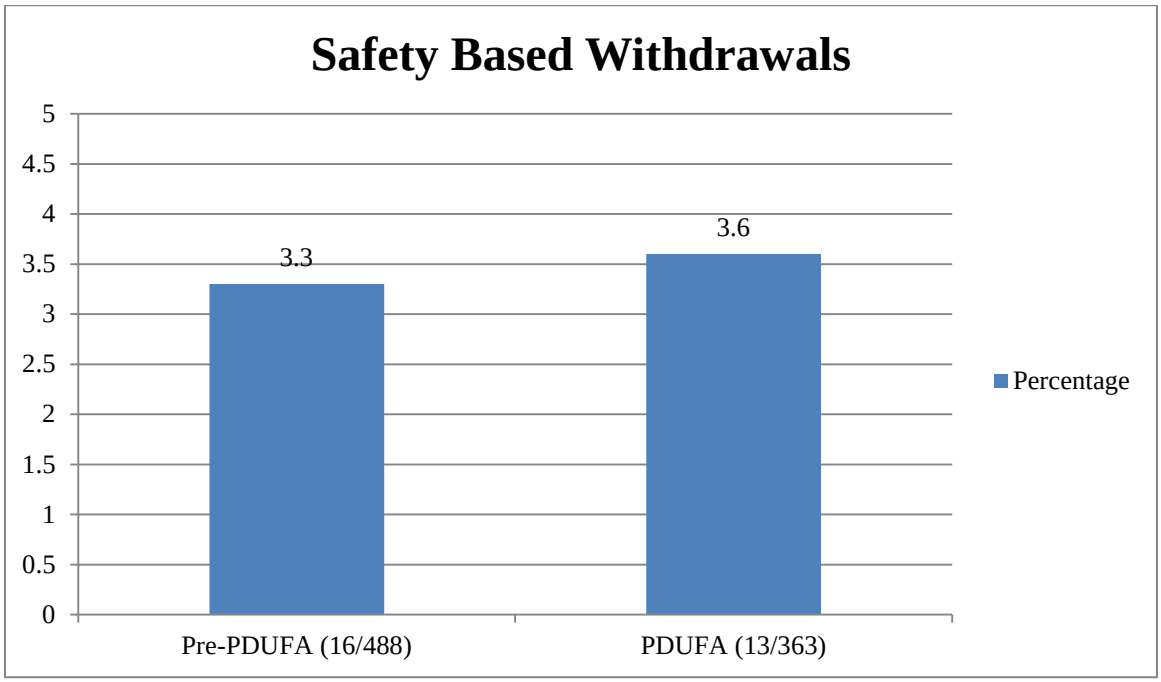

Figure 2 adapted from "Improving Public health through human Drugs, Centre for Drug Evaluation and research." from http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM121704.pdf

Purpose

The purpose of this project is to determine if Priority review of drugs results in a higher frequency of market withdrawals when compared to drugs approved through standard review.

The percent of drugs approved under a standard review that were removed from the market due to safety reasons and the percent of drugs approved under a priority review that were removed from the market due to safety reasons since the beginning of user fees will be considered for this research.

Methods

As the PDUFA program began in 1992, the drugs that have been approved during the time period of 1992-2010 will be considered for this research.

FDA Annual Reports indicate the number of drugs that have been withdrawn from the market and that were approved during the years 1992-2010.The number of Priority review drugs and number of Standard review drugs that have been approved from 1992-2010 and withdrawn from the market was determined by looking at the information available in CDER annual reports and on FDA website.

The statistical significance of the hypothesis “Does Priority Review Result in a Higher Frequency of Drug Withdrawals from the Market than Standard Review?” will be determined by Chi Square test of significance.

Results

Twenty drugs that had been approved during the years 1992-2010 were later withdrawn from the market. Table 2 shows the drugs that were withdrawn, the reason for withdrawal, the approval year, the year withdrawn and review process under which the drug was approved.

Table 1. Drugs Withdrawn from the US Market From 1992-2010

Drug	Reason For Withdrawal	Review Process	Year Withdrawn In US	Year Approved
Omniflox® (Temafloxacin)	Allergic Reactions And Cases Of Hemolytic Anemia	Standard Review	1992	1992
Manoplax® (Flosequinan)	Increased Risk Of Hospitalization Or Death	Standard Review	1993	1993
Alredase ® (Tolrestat)	Severe Hepatotoxicity	Standard Review	1998	1997
Posicor® (Mibefradil)	Dangerous Interactions With Other Drugs	Standard Review	1998	1997
Tasmar® (Tolcapane)	Hepatotoxicity	Standard Review	1998	1998
Raxar® (Grepafloxacin)	Prolonged QT Interval	Standard Review	1999	1997
Rezulin® (Troglitazone)	Withdrawn Because Of Risk Of Hepatotoxicity	Priority review	2000	1997
Propulsid® (Cisapride)	Risk Of Cardiac Arrhythmias	Standard Review	2000	1993
Baycol® (Cerivastatin)	Rabdomylosis	Standard	2001	1997
Raplon® (Rapicuronium)	Bronchospasm	Standard	2001	1999
Orlaam®(Levomethadyl)	Serious Cardiac Adverse Events	Priority	2003	1993
Vioxx® (Rofecoxib)	Heart Attacks, Heart Strokes	Priority	2004	1999
Bextra® (Valdecoxib)	Fatal Cardio Vascular Events	Standard	2005	2001
Trasylol® (Aprotinin)	Renal Toxicity.	Priority	2007	1998

Drug	Reason For Withdrawal	Review Process	Year Withdrawn In US	Year Approved
Zelnorm® (Tegaserod maleate)	Heart Attacks ,Stroke, Angina	Priority	2007	2002
Meridia® (Sibutramine)	Risks For Heart Disease	Standard	2010	2000
Raptiva® (Efalizumab)	Progressive Multifocal Leukoencephalopathy (PML)	Standard	2009	2003
Mylotarg® (Gemtuzumab ozogamicin)	Death In Cancer Patients	Priority	2010	2000
Xigris® (Drotrecogin alfa)	Failed To Show A Survival Benefit For Patients With Severe Sepsis And Septic Shock.	Standard	2011	2001
Neutrospec® (Technitium (99m tc) fanolesomab)	Serious And Life-Threatening Cardiopulmonary Events	Standard	2005	2004

The details of the drugs mentioned in the above table are listed in Appendix: Summary of Drugs Withdrawn From Market

Rezulin® (Troglitazone), Orlaam®(levomethadyl),Vioxx®(rofecoxib), Trasylol® (aprotinin), Zelnorm® (tegaserod maleate), Mylotarg® (gemtuzumab ozogamicin), were approved through priority review during the years 2001-2010. The total number of drug approvals through standard review and priority review from the year 1992-2010 were 1332 and 357 respectively. The number of drugs withdrawn was 6 and 14 belonging to priority and standard review. (See Table 2.)

Table 2. Drugs Approved and Withdrawn From The US Market from 1992-2010

Year	No Of Drugs Approved As Priority Review	No Of Drugs Approved As Standard	No Of Priority Review Drugs Withdrawn	No Of Standard Review Drugs Withdrawn
1992	8	82	0	1
1993	19	51	2	1
1994	16	45	0	0
1995	16	67	0	0
1996	29	102	0	0
1997	20	101	0	5
1998	25	65	0	1
1999	28	55	1	1
2000	20	78	1	1
2001	10	56	0	2
2002	11	67	1	0
2003	14	58	0	1
2004	29	89	0	1
2005	22	59	0	0
2006	21	80	0	0
2007	23	55	0	0
2008	18	70	0	0
2009	13	75	0	0
2010	15	77	0	0

Chi square analysis of these data tests the hypothesis that priority reviews of drugs results in more number of drug withdrawals from market for safety reasons when compared to standard review drugs.

Process	Approvals	Withdrawals
Priority Review	357	5
Standard Review	1332	15

Chi-square: 0.177
Degrees of freedom: 1
p-value: 0.673

Chi square analysis of the above data resulted in a probability of 0.673 which is not statistically significant. Therefore, there is no evidence statistically that the priority review of drugs resulted in more market withdrawals.

Discussion

The number of NDAs approved under Standard and Priority review from the years 1992-2010 were1332 and 357 respectively. The number of drugs under standard and priority review that were withdrawn from the market for safety reasons was 6 and 14, respectively. There is no significant difference in the rate of market withdrawal for safety reasons between drugs approved under priority review versus those approved under standard review.

Priority review of drugs has been granted to reduce the time to approve a drug with significant medical advance. In 1992, under the Prescription Drug User Act (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times – Standard Review and Priority Review. A Priority Review designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review) (Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review, 2013).

Only 1.6% (6) of the total priority review drugs have been withdrawn from the market which were approved between 1992-2010. The number of drugs that was withdrawn were 15 out of 1332 drugs approved as standard review. The percentage of the standard drugs withdrawn from the market is 1.12%; the percentage of priority review drugs was about 1.6%. Priority review of drugs does not result in a higher frequency of market withdrawals than standard reviews.

Conclusion

Based on the analysis of the number of priority and standard drugs withdrawn from market due to safety reasons there is no significant difference in the rate of market withdrawal between these two classes of drugs.

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Appendix: Summary of Drugs Withdrawn From Market

1. Omniflox® (Temafloxacin)

Temafloxacin is a class of synthetic oral fluroquinolones broad spectrum antibiotics that are used in the treatment of infections of lower respiratory tract, skin, prostate and urinary tract infections. It was approved in January 1992 (Recalling of Omniflox (Temafloxacin) Tablets, 1992).

Reason for Withdrawal: Abbott laboratories voluntarily withdrew the drug from the market in June 1992. There have been multiple incidents of adverse events after the drug was in the market. There were more than 50 adverse events reported out of which 3 constituted deaths of the patients that were administered the drug. Many cases of hemolytic anemia were observed in the patients who took Omniflox. Other adverse events that were reported were allergic reactions which were fatal, kidney dysfunction and liver dysfunction.

2. Manoplax® (Flosequinan)

It is a direct vasodilator administered orally for the treatment of patients with congestive heart failure in patients who are not responsive to digitalis or ACE inhibitors. It was approved in the year 1992.

Reason for Withdrawal: It was withdrawn from the market due to its increased adverse events and hospitalizations. It was withdrawn from the market due to safety concerns in the year 1993

3. Alredase ® (Tolrestat)

It is used in the treatment of certain diabetic complications. It was approved in the year 1997. It was manufactured by Wyeth pharmaceuticals.

Reason for Withdrawal. Alredase was voluntarily withdrawn from the market in 1998 due its severe Liver toxicity and death.

4. Posicor® (Mibefradil)

Posicor is a drug that was used in the treatment of Hypertension and angina pectoris. It was approved in the year 1997. It is a calcium channel blocker. It was manufactured by Roche Laboratories.

Reason for Withdrawal: "Posicor was withdrawn from the market in 1998 due to its fatal interactions with 25 drugs which included antibiotics, antihistamines and cancer drugs" (SoRelle, 1998). Initially this drug was labelled that this drug should not be taken along with few drugs that increase the enzyme-inhibiting properties of Posicor. Later it was found that Posicor causes such effects with more than 25 drugs which made FDA to request the company to voluntarily withdraw the drug from the market. The company as a result of this voluntarily withdrew Posicor from the market.

5. Tasmar® (Tolcapane)

Tasmar is used in the treatment Parkinson's disease. It is administered in combination with Levadopa or Carbidopa. It was introduced into the US market in March 1998.

Reason for Withdrawal: Tasmar was withdrawn from the market in November 1998 due to hepatotoxicity.

6. Raxar® (Grepafloxacin)

Raxar is a fluroquinolone antibiotic indicated for the treatment of infections caused by strains of bacteria susceptible to grepafloxacin in the following diseases: community-acquired pneumonia; acute bacterial exacerbations of chronic bronchitis; uncomplicated gonorrhea (urethral in males and endocervical and rectal in females); non-gonococcal urethritis and cervicitis (Withdrawal of Product: RAXAR((grepafloxacin HCl) 600 mg Tablets, 400 mg Tablets, and 200 mg Tablet, 1999). It was approved in the year 1997. It was marketed by the company GlaxoSmithKline.

Reason for Withdrawal: The drug was associated with the risk of torsade de pointes a very rare but serious ventricular arrhythmia. The number of cases that were reported was not high and the chances of this adverse event were very rare but the company voluntarily withdrew the drug as the Risk to Benefit ratio suggested that the drug be withdrawn from the market. Also there were other alternate medications available.

7. Rezulin® (Troglitazone)

Troglitazone (Rezulin) is a drug that is used to treat type 2 diabetes. It was introduced to the US market in the year 1997 by Parke-Davis.

Reason for Withdrawal: The Drug was withdrawn from the market in the year 2000. The data collected from the premarket clinical trials and also safety data after the drug was marketed show that the drugs causes more risk to the liver when compared to other alternatives available in the market (Rezulin to be Withdrawn from the Market, 2000). Therefore the company has voluntarily withdrawn the drug from the market.

8. Propulsid ® (Cisapride)

Propulsid is oral tablet approved in the year 1992. It is used in the treatment of gastrointestinal reflux disease. Cisapride is a prokinetic agent that was approved to treat symptomatic nocturnal heartburn due to GERD. The NDA was submitted in the year 1991 by Janssen Research Foundation.

Reason for Withdrawal: Cisapride was withdrawn from the market in the year 2000 as the drug was associated with causing cardiac arrhythmias which resulted in few deaths.

9. Baycol® (Cerivastatin)

This drug was used as cholesterol lowering agents and also preventing Cardio vascular disease in obese patients. This drug was approved in the year 1997. It was manufactured by Bayer Pharmaceuticals.

Reason for Withdrawal: The drug was withdrawn from the market in 2001"due to increasing reports of side effects involving muscular weakness (rhabdomyolysis). Fatal rhabdomyolysis associated with Baycol have been reported most frequently when used at higher doses, when used in elderly patients, and particularly, when used in combination with gemfibrozil (LOPID and generics), another lipid lowering drug" (Baycol (cerivastatin sodium tablets) Aug 2001, 2001)

10. Raplon® (Rapicuronium)

RAPLON (Rapacuronium bromide) is a drug which was used as an adjunct to general anesthesia for surgical procedures like tracheal intubation and skeletal muscle relaxation. It was approved by FDA in the year 1999. The manufacturer of this drug is Organon Company.

Reason for Withdrawal: The reason for withdrawal of the drug was due to fatalities and also serious bronchospasms. It was withdrawn in the year 2010.

11. Orlaam® (Levomethadyl)

Orlaam is a synthetic opioid agonist solution used to manage opiate dependency for opiate addicted patients who do not respond to other available alternative medicines. It was approved as a priority review drug by the FDA in the year 1993. It was manufactured in the US by Roxane Laboratories.

Reason for Withdrawal: Orlaam was withdrawn from the market as many serious cardiac adverse events such as QT interval prolongation, Torsades de Pointes and cardiac arrest (Safety:Orlaam (levomethadyl acetate hydrochloride), 2003). It was withdrawn in the year 2003.

12. Vioxx® (Rofecoxib)

Vioxx is a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID). Vioxx is also related to the nonselective NSAIDs, such as ibuprofen and naproxen. Vioxx is a prescription medicine used to relieve signs and symptoms of arthritis, acute pain in adults, and painful menstrual cycles (Vioxx Safety Information, 2009).

Vioxx was approved as a priority review drug in the year 1999.Vioxx was granted a priority review as it showed therapeutic advantage over the other drugs that were available in the market.

Reason for Withdrawal: Vioxx was voluntarily withdrawn from the market by Merck Pharmaceuticals. Merck did this as the result of findings of the VIGOR study which showed high cardio vascular risks to the patients. “The study, involving 1.4 million Americans from 1999 to September 2004, showed that Vioxx-treated patients had a 34 per cent greater chance of

developing coronary heart disease when compared with other drugs" (Pichereau, 2005).Vioxx was approved as it was considered a safer alternative when compared to other similar drugs as it caused fewer gastrointestinal side effects when compared to other option available in the market.

Though the NDA showed evidence of cardiovascular adverse events such as hypertension and thromboembolic events in subjects taking Vioxx for longer durations this was considered similar to other comparator NSAIDS.

13. Bextra® (Valdecoxib)

Bextra belongs to the class of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). Bextra is used to reduce pain, inflammation, and stiffness caused by osteoarthritis and adult rheumatoid arthritis.It was approved in the year 2001. It was manufactured by Pfizer, Inc.

Reason for Withdrawal: Pfizer voluntarily withdrew the drug Bextra from the market as it was associated with cardiovascular adverse events, life threatening skin reactions including deaths in patients using Bextra. There was also no proof of advantages of Bextra over the other alternate NSAIDs available in the market.

14. Trasylol® (Aprotinin)

This is a drug which was approved in the year 1998. It is used as a clotting agent which prevents bleeding during heart surgeries. The review process under which the drug was approved was priority review. It was manufactured by Bayer Pharmaceuticals.

Reason for Withdrawal: This drug was associated with kidney failure, heart failure, heart attacks and strokes in patients who were administered trysalol during surgery. 22,000 lives could have been saved if Trysalol was withdrawn earlier. Bayer withdrew trysalol in the year 2007.

15. Zelnorm® (Tegaserod maleate)

It is a drug used for the short-term treatment of women with irritable bowel syndrome with constipation and for patients younger than 65 years of age with chronic constipation (Safety-Zelnorm (tegaserod maleate), 2007). The review process under which the drug was approved was priority review. It was approved in the year 2002 and was manufactured by Novartis.

Reason for Withdrawal: FDA analysis of safety data pooled from 29 clinical trials involving over 18,000 patients showed an excess number of serious cardiovascular adverse events, including angina, heart attacks, and stroke, in patients taking Zelnorm compared to patients given placebo (Safety-Zelnorm (tegaserod maleate), 2007). It was withdrawn from the market in the year 2007.

16. Mylotarg® (Gemtuzumab ozogamicin)

Mylotarg is used for the treatment of acute myeloid leukemia (AML). It was approved by the FDA in the year 2000. The review process under which the drug was approved was priority review.

Reason for Withdrawal: Pfizer withdrew the drug from the market in the year 2010. The decision was based on the studies that were conducted after the drug got approved. The studies showed that upon adding Mylotarg to the chemotherapy that the patients received did not show any additional clinical benefit. Also there were many deaths that were reported in the patients that were given Mylotarg.

17. Meridia® (Sibutramine)

Meridia is an oral anorexic agent approved by FDA in the year 1997. Meridia is used together with diet and exercise to treat obesity. It is mainly used in patients with obesity that is related to high cholesterol, diabetes or high blood pressure. The NDA was submitted by Knoll Pharmaceutical Company (Abbott Laboratories) on August 7, 1995.

"The approval for Meridia was based on the clinical data that showed that the drug resulted in at least 5% of their body weight than people on placebo" (Meridia (sibutramine): Market Withdrawal Due to Risk of Serious Cardiovascular Events, 2013)

Reason for Withdrawal: Meridia was withdrawn from the market in 2010 due its serious cardiovascular events. (FDA-Safety Communication Meridia, 2010).

18. Raptiva® (Efalizumab)

This drug is used to treat patients with Psoriasis and autoimmune diseases. It was approved in the year 2003.

Reason for Withdrawal: "Genentech's decision to withdraw is based on the finding of an association with the use of Raptiva and an increased risk of progressive multifocal leukoencephalopathy (PML), a rare and usually fatal disease of the central nervous system" (Drug Safety:Efalizumab (marketed as Raptiva) Information, 2009).

19. Xigris® (Drotrecogin alfa)

Xigris was indicated for the reduction of mortality in adult patients with severe sepsis who have a high risk of death.

Reason for its withdrawal: This drug was withdrawn from the market due to its failure to show a survival benefit for patients with severe sepsis and septic shock. The reason it was withdrawn not due to having adverse effects but due to lack of efficacy.

20. Neutrospec® (Technitium (99m tc) fanolesomab)

Neutrospec is a monoclonal antibody used to aid in the diagnosis of appendicitis. It was approved in the year 2004 and was manufactured by Palatin Technologies.

Reason for Withdrawal. Neutrospec was withdrawn from the market as it caused cardiac complications in patients within a few minutes of its use. It was withdrawn in the year 2005.