



Tufts Center for the Study of Drug Development

Impact REPORT

ANALYSIS AND INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES

Drug safety withdrawals in the U.S. not linked to speed of FDA approval

New product approval times do not correlate with degree of safety

- The number of drugs withdrawn for safety reasons since 2000, as a share of total approvals, has dropped in half since the 1980s, following a slight increase in the 1990s.
- The rate of drug safety withdrawals, based on year of product approval, has not increased since the user fee era began in 1993.
- Faster approval times do not correlate with increased drug safety withdrawals, when grouped either by decade of drug approval and by therapeutic class.
- Three therapeutic classes account for 70% of drug withdrawals between 1980 and 2005.

During the last few years, critics of the U.S. Food and Drug Administration (FDA) and the research-based drug industry have asserted that drug safety in the United States has deteriorated. It is claimed that the adoption of user fees in 1993 — whereby drug developers pay the FDA for the regulatory review of new drug applications — has weakened FDA safety standards. In addition, critics allege that speeding the approval process has led to more withdrawals of approved drugs for safety reasons. Periodic, well-publicized withdrawals of high profile prescription drugs have also heightened public awareness of and concern about drug safety issues.

Has there been a dramatic increase in the number of safety withdrawals in the U.S. since implementation of the *Prescription Drug Fee User Act of 1992* (PDUFA)? Do faster approval times increase the likelihood of safety problems?

To help answer these questions, Tufts CSDD recently undertook an analysis of drugs withdrawn from the U.S. market since 1980 for safety reasons. We found that the answer to both questions is no. The evidence to date fails to establish a relationship between passage of PDUFA and the rate of safety withdrawals, or between FDA approval times and drug safety. Because many factors influence drug safety, Tufts CSDD will continue to study and report on this important issue.

The rate of drug withdrawals for safety reasons has dropped in half since the 1980s

Drug Safety Withdrawals By Decade

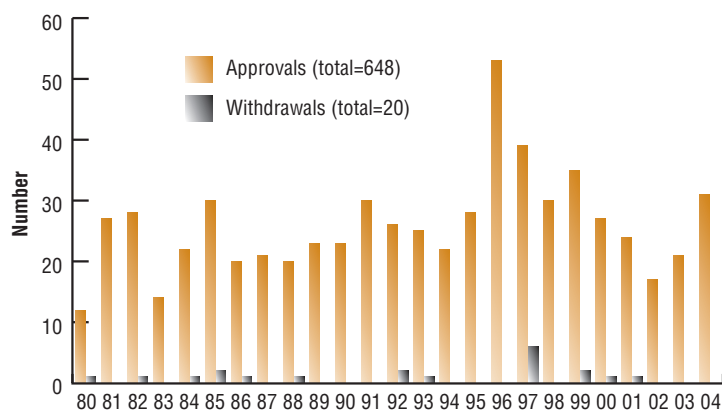
Year of Approval	Total NME Approvals	Total Safety Withdrawals	Share
1980-89	217	7	3.2%
1990-99	311	11	3.5%
2000-04	120	2	1.6%

Source: Tufts Center for the Study of Drug Development

- Although there were 4 more safety withdrawals in the 1990s, compared to the 1980s, there was a greater number of NME approvals (94) in the latter decade and a modest increase in the safety withdrawal rate.
- Two of the 11 drugs withdrawn in the 1990s received FDA approval before the user fee era began in 1993.
- Following a brief increase in the 1990s, the safety withdrawal rate in the U.S. dropped in half in 2000-04 compared to the 1980s.
- Note that some drugs approved in recent years have not been on the market long enough to uncover serious safety problems, and may eventually be withdrawn for safety reasons.

Rate of drug safety withdrawals has not increased since the user fee era began in 1993

Rates of New Drug Approvals and Withdrawals



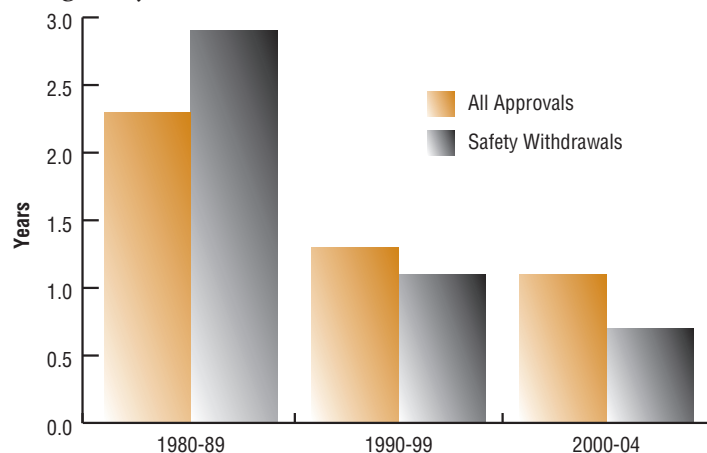
Note: Withdrawals listed by year of product approval.

Source: Tufts Center for the Study of Drug Development

- Nearly half — 9 of 20 — of the drugs withdrawn for safety reasons between 1980 and 2005 were approved before the user fee era began in 1993.
- Average time between date of FDA approval and date of subsequent safety withdrawal dropped from 3.7 years in the 1980s to 1.4 years in the 1990s, to 0.7 years in the current decade. (Potential future withdrawals of products approved in the current decade will cause this last number to increase.)
- Longer approval times do not assure greater safety. The average approval time of 2.14 years for drugs withdrawn since 1980 compares to 2.08 years for all NME approvals during that time.

Faster approval times do not correlate with increased drug safety withdrawals

Median Approval Times for Safety Withdrawals vs All Drugs – By Decade



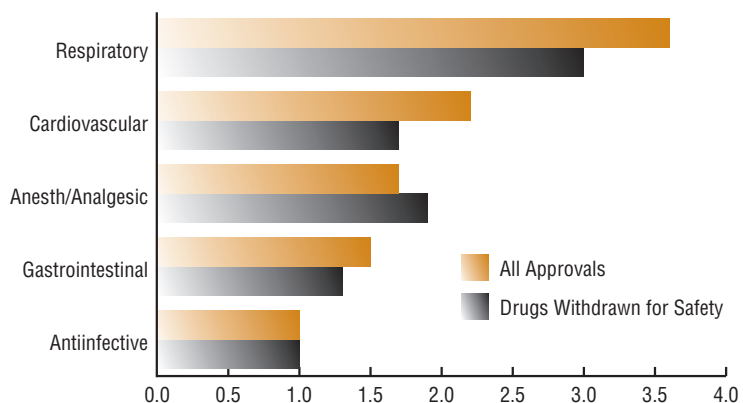
Source: Tufts Center for the Study of Drug Development

- Drugs withdrawn from the U.S. market in the 1980s took longer to win FDA approval than all drugs approved during that decade: 2.9 years vs. 2.3 years.
- While drugs withdrawn during the 1990s had slightly shorter approval times than all drugs approved during that time — 1.1 vs. 1.3 years — the difference is minor.
- During the first half of the current decade, only two drugs had been withdrawn from the U.S. market for safety reasons.

NOTE: See pg. 4 for full listing of all drugs withdrawn.

Faster approval times also do not correlate with safety withdrawals within therapeutic class

Median Approval Times for Safety Withdrawals vs All Drugs — By Therapeutic Class



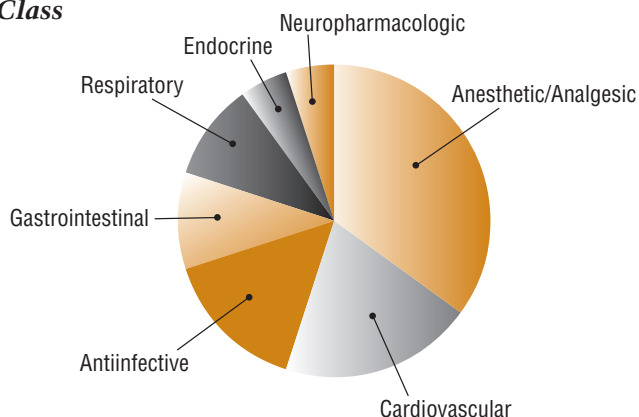
Note: Median values for all approvals are for range of years of safety withdrawals.

Source: Tufts Center for the Study of Drug Development

- When assessing the 20 drugs withdrawn from the U.S. market for safety reasons by therapeutic category between 1980 and 2004, no trend emerges between speed of approval and withdrawal.
- Respiratory, cardiovascular, and gastrointestinal drugs withdrawn for safety reasons, on average, had slightly shorter approval times compared to all drugs that had won market approval in those classes.
- Antiinfective and anesthetic/analgesic drugs withdrawn for safety reasons had the same or slightly longer median approval times, respectively, than all drugs within the same class.

Three therapeutic classes account for 70% of drug withdrawals between 1980 and 2005

Distribution of Safety Withdrawals — By Therapeutic Class



Source: Tufts Center for the Study of Drug Development

- Fourteen, or 70%, of the drugs withdrawn from the U.S. market between 1980 and 2005 were anesthetic/analgesic, cardiovascular, and antiinfective drugs.
- Only one endocrine and one neuropharmacologic drug were withdrawn during the same period.
- Ten of the 20 drugs withdrawn were removed from the market due to cardio/renal toxicities; four were withdrawn because of hepatotoxicity.
- During the same time, one drug was withdrawn for each of the following: dermatologic, respiratory, musculoskeletal, and gastrointestinal toxicities; two drugs were withdrawn for generalized toxicity.

A number of proposals have been offered to address drug safety issues

- The *FDA Safety Act of 2005*, proposed in the U.S. Senate by Senators Charles E. Grassley (R-Iowa) and Christopher J. Dodd (D-CT), would create an independent safety board. This board, to be called the Center for Postmarket Drug Evaluation & Research, would:
 - Pull drugs from market using “expedited procedures”
 - Require sponsors to conduct postmarket clinical and observational studies
 - Levy fines for failing to complete post-market study commitments
 - Require labeling changes
 - Require other risk management techniques (e.g., restricted distribution)
 - Require sponsors “to monitor sales and usage. . . to detect unsafe use”
 - Review promotional material
 - Have an additional limited pre-approval review function
 - Require the FDA to consider a product’s “risk-to-benefit profile”
- The FDA has also proposed creating an independent Drug Safety Oversight Board to oversee the management of drug safety issues. The board would provide emerging information to health providers and patients about the risks and benefits of medicines.

Safety withdrawals: 1980 – 2005

Listed here are all FDA-approved drugs that were subsequently withdrawn from the U.S. market by the sponsoring company for safety reasons from 1980 through the first quarter of 2005.

Drug	Approved	Therapeutic Class	Rating*	Approval Phase (years)
Zomax (zomepirac)	1980	NSAID	P	1.9
Oraflex (benoxaprofen)	1982	NSAID	S	2.2
Merital (nomifensine)	1984	antidepressant	S	6.0
Suprol (suprofen)	1985	NSAID	S	7.2
Seldane (terfenadine)	1985	antihistamine	P	2.2
Enkaid (encainide)	1986	antiarrhythmic	P	2.9
Hismanal (astemizole)	1988	antihistamine	S	3.8
Omniflox (temafloxin)	1992	antiinfective	S	2.2
Manoplax (flosequinan)	1992	vasodilator	S	2.2
Propulsid (cisapride)	1993	gastrointestinal	S	1.9
Duract (bromfenac)	1997	NSAID	S	2.5
Posicor (mibefradil)	1997	antihypertensive	S	1.3
Raxar (grepafloxacin)	1997	antiinfective	S	1.0
Trovan (trovafloxacin)**	1997	antiinfective	S	1.0
Rezulin (troglitazone)	1997	antidiabetic	P	0.5
Baycol (cerivastatin)	1997	statin	S	1.0
Raplon (rapacuronium)	1999	anesthetic	S	1.1
Vioxx (rofecoxib)	1999	NSAID (Cox-2)	P	0.5
Lotronex (alosetron)**	2000	gastrointestinal	P	0.6
Bextra (valdecoxib)	2001	NSAID (Cox-2)	S	0.8

* P = Priority Review; S= Standard Review

** Subsequently re-introduced to the market with restricted labeling

Definition of terms

NME — New Molecular Entity. Refers to a newly developed compound, whose active ingredient has not been previously approved in the U.S. The term was coined by FDA for use in their published statistical reports.

User fee era — Years following passage of the *Prescription Drug User Fee Act of 1992* (PDUFA), authorizing the FDA to collect user fees for regulatory review of new drug applications. These fees are earmarked to hire additional reviewers and improve the drug review process. PDUFA was reauthorized in 1997 and again in 2002.

About the Tufts Center for the Study of Drug Development

The Tufts Center for the Study of Drug Development at Tufts University provides strategic information to help drug developers, regulators, and policy makers improve the quality and efficiency of pharmaceutical development, review, and utilization. Tufts CSDD conducts a wide range of in-depth analyses on pharmaceutical issues and, in addition, hosts symposia, workshops, and public forums on related topics.

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