

Sample List of Drugs Withdrawn for Safety Reasons or BBWed, with details and sources.

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A general note: It is very important, in pointing to these examples of pre-deadline approvals that later encountered safety problems, to understand the limitations of a statistical analysis. A statistical analysis of cases can only shed light on population-level relationships that prevail among the cases; it cannot allow us to make inferences about anyone case. Example: Edward Krumbiegel (my late grandfather, former health commissioner of Milwaukee) was a life-long smoker and died of a heart attack in his late 80s. His smoking may have caused his heart attack, and we know from statistical studies that smoking is associated with heart disease, but no statistical study can tell us whether Krumbiegel's smoking in particular caused his heart attack and his death.

Nonetheless, these examples may help to flesh out the relationships observed in the study. If "predead" is 1 for the drugs below, then the drug was coded as a "just-before-deadline" approval according to the protocol of the NEJM study.

Examples:

Raxar

	genenam	trname	subdate	appdate	priority	predead
1545.	Grepafloxacin Hydrochloride	Raxar	11/8/1996	11/6/1997	0	1

Grepafloxacin hydrochloride is a fluorouracil antibiotic. Note that this was submitted before the FDAMA of 1997 was passed, and so falls under the 12-month deadline of "PDUFA I." Raxar was withdrawn in November 1999 for reasons related to cardiovascular problems. Source: Lasser, JAMA (2002). [Reference in the [NEJM](#) paper.]

Baycol

	genenam	trname	subdate	appdate	priority	predead
1560.	Cerivastatin Sodium	BAYCOL	6/26/1996	6/26/1997	0	1

In October 2001, Bayer Pharmaceuticals voluntarily withdrew its cholesterol-lowering drug cerivastatin, because of reports of 31 deaths from rhabdomyolysis. Source: Pharmaprojects, Harvard University NME database.

Rezulin

	genenam	trname	subdate	appdate	priority	predead	
1556.	Troglitazone	Rezulin	8/1/1996	1/29/1997	1	1	

This drug, a Thiazolidinedione antidiabetic, was withdrawn in the UK for reasons related to its hepatotoxicity. BBW added in the U.S., then it was withdrawn, then re-introduced. Source, Fung et al, DIJ (2001); Lasser et al, JAMA (2002). [Reference in the NEJM paper.]

Vioxx

	genenam	trname	subdate	appdate	priority	predead	
1636.	Rofecoxib	Vioxx	11/23/1998	5/20/1999	1	1	

This drug and its problems are now well known, but what is not commonly known is that it was a priority NME. Withdrawn September 2004 after a RCT for colon polyps evinced a trebling of myocardial infarction rates in the treatment group compared with control group. Source: Pharmaprojects, Harvard University NME database.

Bextra

	genenam	trname	subdate	appdate	priority	predead	
1692.	Valdecoxib	Bextra	1/16/2001	11/16/2001	0	1	

Bextra was withdrawn from the worldwide market in 2005. Source: Pharmaprojects, Harvard University NME database.

Trovan

	genenam	trname	subdate	appdate	priority	predead	
1566.	Trovafloxacin Mesylate	Trovan	12/30/1996	12/18/1997	0	1	

Like Raxar, this is a fluorouracil antibiotic. In December 1999 a BBW was added for hepatic toxicity. Source: Lasser et al, JAMA (2002). [Reference in the NEJM paper.]

Baraclude

	genenam	trname	subdate	appdate	priority	predead	
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1749. | Entecavir Baraclude 9/30/2004 3/29/2005 1 1 |

Baraclude, approved for hepatitis B infection, has been hit with what one journalist calls a "litany of warnings." Most recently, in August 2007, it received a black-box warning for patients co-infected with HIV, as use of the drug may worsen HIV infection.

NOTE: Not coded as BBW in our database but also of interest: **Avandia** (rosiglitazone). The central NEJM study was published in May 2007, after our paper was first submitted. The BBW for Avandia was not recommended until August 2007, and revised labeling was not finalized until November 2007, at which point our paper was in later stages of review and we felt it would be inappropriate to change coding in the middle of review. Note that if Avandia is recoded as a BBW, our findings only get stronger, as it was a pre-deadline approval.