Analysis of Evidence used to Justify Drugs Withdrawn from the Market for Safety Reason in USA from 1976 to 2010

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Evidence Live 2016

Conflicts of Interest

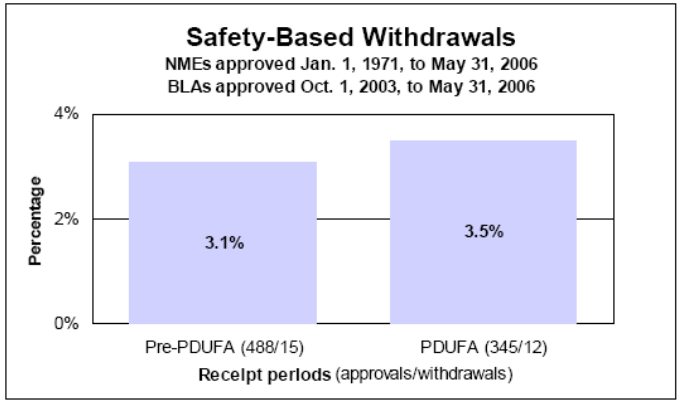
- No conflict of interest with Drug Companies to declare
- No accademic conflict of interest to declare

Aims of the review

- Identify the evidence cited by the FDA at time of withdrawal
- Classify these evidence according to their study design
- Observe the trends of the use of the different study designs over the period under study
- Generate a mathematical model for the length of marketing of this cohort of DWSR
- Review the evidence using a comparative study design according to the GRADE framework

Delimiting a Research Area to Study the use of Evidence in Drug Safety

- Selecting a geographical area
  - FDA: largest market under a unique regulatory authority
- Generating a list of DsWSR
  - Report to the Nation series up to 2005
  - Yearly CDER Updates



Safety-Based Drug Withdrawals

In some cases, there is an intrinsic property of a drug that makes it necessary to withdraw the drug from the market for safety reasons. The rates of safety-based withdrawals of new molecular entities are similar for an earlier period before we collected user fees and for the period, beginning Oct. 1, 1992, when we collected user fees. Our time periods are based on when we received an application rather than when we approved it. Beginning Oct. 1, 2003, approvals include new therapeutic biologics. Applications exempt from user fees are also counted.

Four safety withdrawals of NMEs or new BLAs in 2005

- *Valdecoxib,* a COX-2 selective non-steroidal anti-inflammatory pain reliever, was withdrawn because it carried an increased risk of serious skin reactions in addition to the risk of heart disease associated with NSAIDs.
- *Pemoline,* a central nervous system stimulant treatment for attention deficit hyperactivity disorder, was withdrawn because it caused fatal and life-threatening liver failure.
- *Natalizumab,* a treatment for multiple sclerosis, was withdrawn because three patients developed a serious viral infection of the brain. It was reintroduced in 2006 with a special restricted distribution program.
- *Technetium (99m Tc) fanolesomab,* a radiological imaging agent for unclear signs and symptoms of appendicitis, was withdrawn for fatal and life-threatening cardiopulmonary arrest occurring shortly after administration.

One non-NME safety withdrawal in 2005

- *Palladone*, a brand of hydromorphone hydrochloride extended-release capsules, was withdrawn because serious and potentially fatal adverse reactions could occur if the drug was taken with alcohol, which harmed the extended-release mechanism and could lead to dose-dumping.

NME safety withdrawals (cont.)

- **Flosequinan**
(1991/1992/1993)
congestive heart failure/
increased deaths
- **Fenfluramine**
(1967/1973/1997)
appetite suppression/
heart valve disease
- **Terfenadine**
(1983/1985/1998)
antihistamine/
fatal arrhythmia
- **Bromfenac**
(**1995**/1997/1998)
pain relief/
liver toxicity
- **Mibefradil**
(**1996**/1997/1998)
blood pressure reduction/
serious drug-drug
interactions leading to
muscle damage and fatal
arrhythmia
- **Grepafloxacin**
(**1997**/1997/1999)
antibiotic/fatal arrhythmia
- **Astemizole**
(1985/1988/1999)
antihistamine/
fatal arrhythmia
- **Cisapride**
(1991/1993/2000)
heartburn/fatal arrhythmia
- **Troglitazone**
(**1996**/1997/2000)
diabetes/liver toxicity
- **Alosetron**
[Remarketed in 2002 with
restricted distribution]
(**1999**/2000/2000)
irritable bowel syndrome/
ischemic colitis, severe
constipation

NME safety withdrawals (cont.)

- **Cerivastatin**
(**1996**/1997/2001)
cholesterol reduction/
muscle damage leading
to kidney failure
- **Rapacuronium**
(**1998**/1999/2001)
anesthetic/severe
breathing difficulty
- **Etretinate**
(1985/1986/2002)
psoriasis/birth defects
- **Levomethadyl**
(**1993**/1993/2003)
opiate dependence/
fatal arrhythmia
- **Rofecoxib**
(**1999**/1999/2004)
pain relief/
heart attack, stroke
- **Valdecoxib**
(**2001**/2001/2005)
pain relief/skin disease
- **Natalizumab**
[Remarketed in 2006 with
restricted distribution]
(**2004**/2004/2005)
multiple sclerosis/
brain infection
- **Technetium (99m Tc) fanolesomab**
(**2000**/2004/2005)
diagnostic aid/
cardiopulmonary arrest
- **Pemoline**
(1969/1975/2005)
ADHD/liver failure

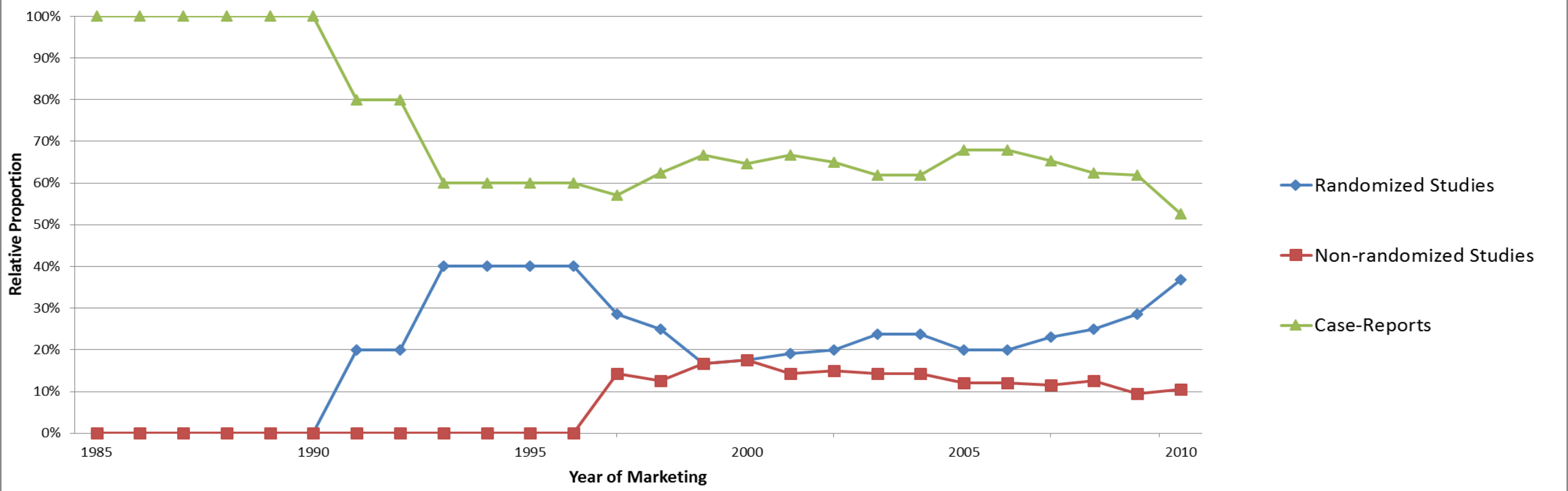
- Withdrawals from 1976 to 2010
- A list of 34 drugs
- Cause stated by the FDA
  - Fatal arrhythmias 8
  - Hepatic toxicity 5
  - Cardiovascular events 3
  - Kidney failure 3
  - Heart valve disease 2
  - Fatal allergy reaction 2

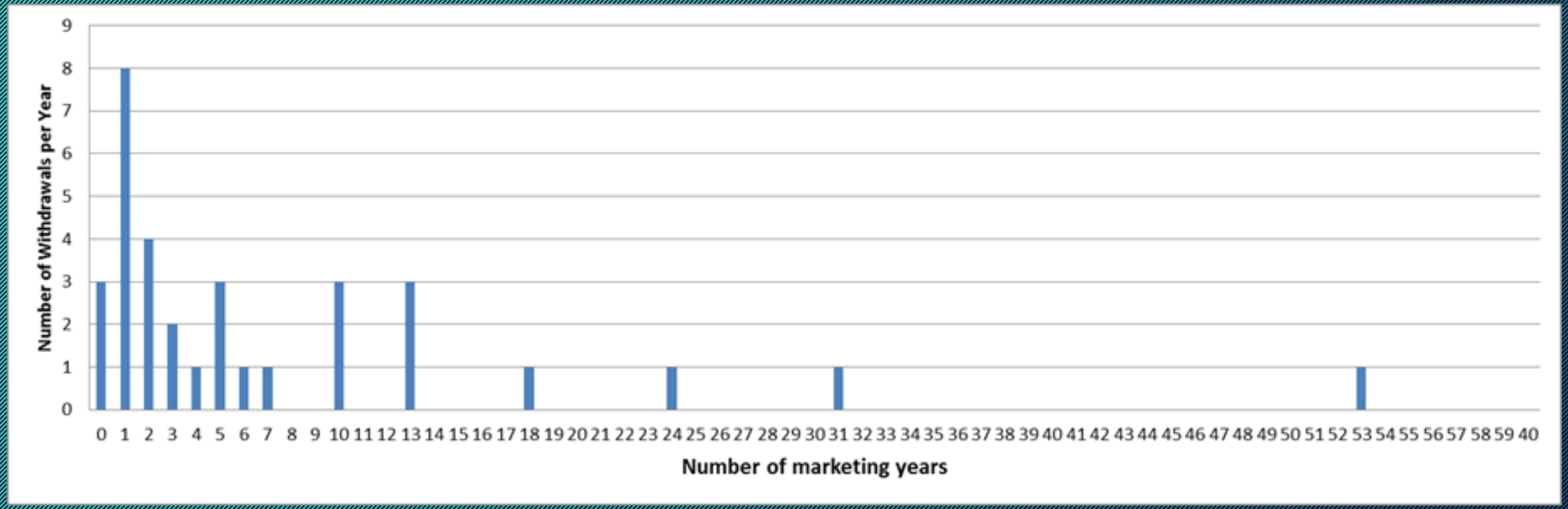
- Study Design Used
  - Comparative Studies alone 6 (18%)
  - Case Report alone 19 (56%)
  - Mixed 7 (21%)

Generic Name	Approval date	Withdrawal date	Indication	Reason for withdrawal
Phenhylpropranolamine[36]	NA by FDA**	11-6-2000	Decongestant	Hemorrhagic Stroke
Propoxylene[37]	12-11-1957	11-19-2010	Pain relief	Fatal arrhythmia
Fenfluramine[38-40]	6-14-1973	9-15-1997	Appetite suppression	Heart Valve Disease
Azarabine[41, 42]	1-1-1975	6-10-1976	Psoriasis	Serious Blood Clot
Pemoline[43]	1-27-1975	10-24-2005	ADHD	Liver toxicity
Ticrynafen[44]	12-1-1979	6-16-1980	Hypertension	Liver Toxicity
Zomepirac[45]	11-1-1980	3-4-1983	Pain relief	Fatal allergy Reaction
Nomifensine[46]	12-31-1980	3-19-1983	Depression	Hemolityc Anemia
Benoxaprofen[47]	4-19-1982	8-5-1982	Pain relief	Liver Toxicity
Terfenadine[42]	5-8-1985	2-1-1998	Antihistamine	Fatal Arrhythmia
Suprofen[48]	12-24-1985	5-15-1987	Pain relief	Acute Kidney Failure
Etretinate[49, 50] §	9-30-1986	9-23-1999**	Psoriasis	Birth Defects
Encainide[51]	12-24-1986	12-16-1991	Arrhythmia	Fatal Arrhythmia
Astemizole[42]	12-29-1988	6-18-1999	Antihistamine	Fatal Arrhythmia
Pergolide[52, 53]	12-30-1988	3-29-2007	Parkinson	Damage to heart valve
Temafloxacin[54]	1-30-1992	6-5-1992	Infection	Kydney Failure
Flosequinan[55]	12-31-1992	7-16-1993	Heart Failure	Increased Death
Levomethadyl[56] §	7-9-1993	8-23-2003	Opiate dependance	Fatal Arrhythmia
Cisapride[57, 58]	7-29-1993	7-14-2000	Heartburn	Fatal Arrhythmia
Troglitazone[59]	1-29-1997	3-21-2000	Diabetes	Liver toxicity
Mibefradil[60]	6-20-1997	6-8-1998	Hypertension	Drug interacion muscle damage, and fatal arrhythmia
Cerivastatin[61]	6-26-1997	8-8-2001	High Cholesterol	Muscle damage and kidney failure
Bromfenac[62]	7-15-1997	6-22-1998	Pain relief	Liver Toxicity
Grepafloxacin[63]	11-6-1997	10-27-1999	Antibiotic	Fatal Arrhythmia
Sibutramine[64, 65]	11-22-1997	10-8-2010	Weight loss	Cardiovascular event
Rofecoxib[66]	5-20-1999	9-30-2004	Pain relief	Heart attack, Stroke
Rapacuronium[67, 68]	8-18-1999	3-27-2001	Anesthesic	Severe breathing difficulty
Alosetron[69, 70]	2-9-2000	11-30-2000	Irritable Bowel Syndrome	Ischemic colitis, Severe constipation
Gemtuzumab [71]	5-17-2000	10-15-2010	Chemotherapy	Fatal Induction toxicity
Valdecoxib[72]	11-16-2001	4-7-2005	Pain relief	Skin disease
Tegaserod [25]	7-24-2002	3-30-2007	Irritable Bowel Syndrome	Increased cardiovascular risk
Efalizumab[73]	10-27-2003	6-8-2009	Psoriasis	Progressive Multifocal Leukoencephalopathy
Technecium Fanolesomab[74]	7-2-2004	12-19-2005	Diagnostic aid	Cardiopulmonary arrest

Country	Time Period	Number of DWSR	Comparative Studies alone	Comparative Studies and Case Reports	Case Report alone
UK & US	1999-2001	11	4 (36%)	3 (27%)	4 (36%)
France	1998-2004	21	2 (10%)	7 (33%)	12 (57%)
Spain	1990-1999	22	4 (18%)	4 (18%)	14 (64%)
Total		54	10 (19%)	14 (26%)	30 (56%)

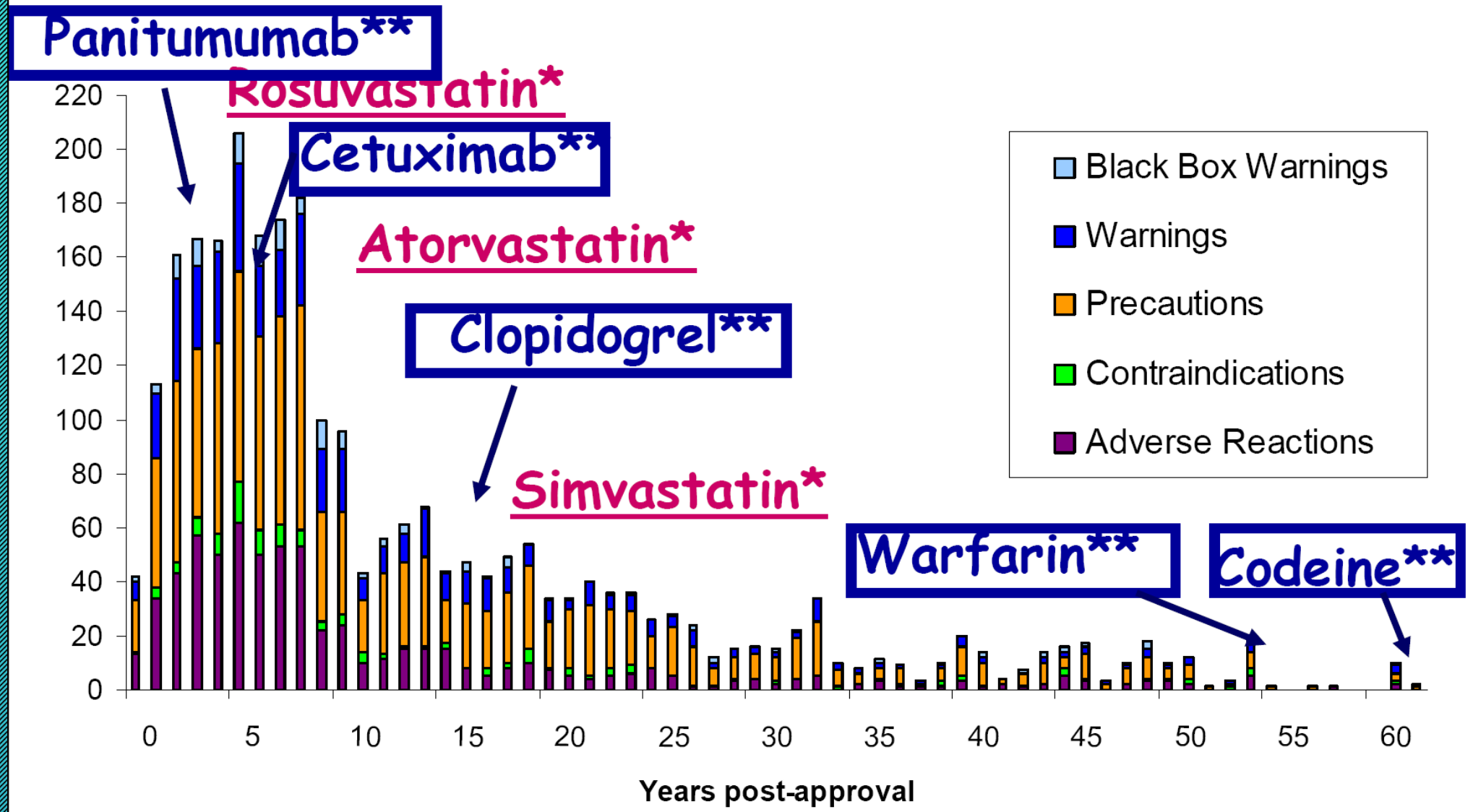
Trends in the use of different study designs (last 10 years of Marketing)




Number of Withdrawals per Year
0
1
2
3
4
5
6
7
8
9
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 40
Number of marketing years

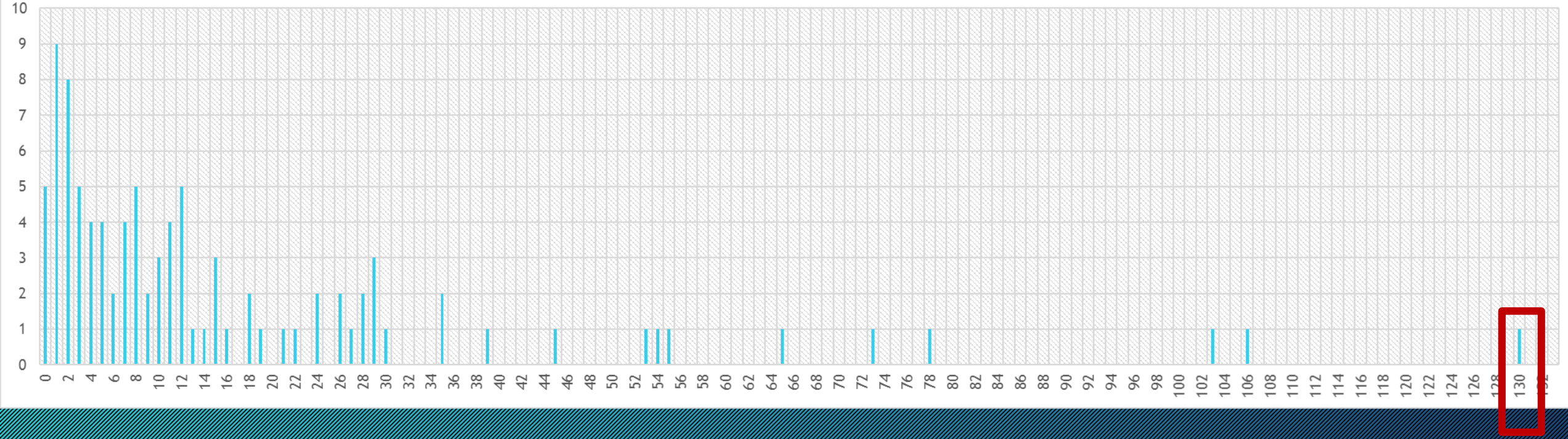
Safety-Related Labeling Changes

(changes made Oct 2002-Aug 2005, n=2645 label changes for 1601 NDA/BLA entries)



*Recent changes (after 2005) **Related to pharmacogenetics

Post Marketing Wtihdrawals because of Deaths in the World



Onakpoya *et al. BMC Medicine* (2015) 13:26

Lognormal Model

DWSR Cohort Proportion (%)	Predicted Post Marketing (Years)
5	0,3
10	0,6
15	0,8
20	1,0
25	1,3
30	1,6
35	1,9
40	2,3
45	2,8
50	**3,3**
55	3,9
60	4,6
65	5,6
70	6,7
75	**8,3**
80	10,4
85	13,7
90	**19,1**
95	31,6
97	43,7
98	55,5
99	80,8

Type 2 Diabetes Drugs available in US Market on the 23rd of June 2016

Meglitinides				
	Repaglinide	Prandin	2013-07-11	3,0
	Nateglinide	Starlix	2009-09-09	6,8
Sulfonylureas				
	Glipizide	Glucotrol	1995-02-27	21,3
	Glimepiride	Amaryl	2005-10-06	10,7
	Glyburide	Diabeta	1992-04-17	24,2
DPP4 Inhibitors				
	Saxagliptin	Onglyza	2016-01-21	0,4
	Sitagliptin	Januvia	2006-10-16	9,7
	Linagliptin	Tradjenta	2011-05-02	5,1
Biguanides				
	Metformin	Glucophage	1995-03-03	21,3
Thialolidinediones				
	Rosiglitazone	Avandia	1999-05-25	17,1
	Pioglitazone	Actos	1999-07-15	17,0
Alpha-glucosinase Inhibitors				
	Acarbose	Precose	1995-09-06	20,8
	Miglitol	Glyset	1996-12-18	19,5
SGLT2 Inhibitors				
	Canagliflozin	Invokana	2013-03-29	3,2
	Dapagliflozin	Farxiga	2014-01-08	2,5
	Empagliflozin	Jardiance	2014-08-01	1,9
Bile Acid Sequestran				
	Closevelam	Welchol	2000-05-26	16,1
Amylin Mimetics				
	Pramlintide	Symlin	2005-03-16	11,3
Incretin Mimetics				
	Exenatide	Byetta	2005-04-28	11,2
	Exenatide Extend	Bydureon	2012-01-27	4,4
	Liraglutide	Victoza	2010-01-25	6,4

Very High Risk Period

High Risk Period

Moderate Risk Period

Low Risk Period

Drug	Cause	Withdrawal	Published	Evidence	Magnitude and accuracy of endpoints	Replicated at time of withdrawal	Placebo	Enpoint
Propoxyphene[37]	Fatal arrhythmia	2010	2010	RCT SE*	ΔQTc** 90% CI 600 mg 29.8 11.7-47.9 900 mg 38.2 19.0-57.4		X	S§
Gemtuzumab Ozogamicin[71]	Fatal induction toxicity	2010	2010	RCT SE	Death RR 4.75 16/283=5.7% vs 4/281=1.4%, P=0.01)[71]		X	PR¶
Sibutramine[64, 76, 77]	Cardiovascular events (CV)	2010	2010	RCT	MI HR 1.28; (95% CI, 1.04 to 1.57; P = 0.02) Stroke : HR1.36; (95% CI, 1.04 to 1.77;) P = 0.03[64]		X	PR
Pergolide[52, 53, 78]	Heart valve disease	2007	2007 2007	Case-Control	Valve regur IRR 7.1 (2.3–22.3) [52]Mitral reg RR 6.3 P= 0.008[53]	X		S
Tegaserod maleate[25]	Cardiovascular events	2007	2007	Systematic review of RCTs	Liftreatning CV events 13/11614 vs 1/7013[25] RR = 7.85		X	PR
Rofecoxib[66, 79, 80]	Cardiovascular events	2004	2000 2004	RCT SE	Thromb events RR 1.92 (95% CI, 1.19 to 3.11; P=0.008)[66] MI RR 2·24 (95% CI 1·24–4·02)[80]	X	X	PR
Phenylpropanolamine[36]	Cardiovascular events	2000	2000	Case-Control	Stroke AOR 15.92 (LCL=2.04, p=0.013)[36]			PR
Rapacuronium[67, 68, 81]	Severe breathing difficulty	2001	1999	RCT	Bronchospasm 10.7% vs 4.1% P=0,021[67]			PR
Cisapride[58, 82]	Fatal arrhythmia	2000	1998 2000	Cohort	IQTc 11/35 TdP 2/35 [58]; 2/100 IQTc [82]	X		S
Troglitazone[59, 83-85]	Hepatic toxicity	2000	1998	Cohort/RCT	Hep dys 43/2510 vs 3/475 Jaundice 2/2510 vs 0[59] Jaundice 1/116 vs 0/116 vs /118[85]			PR
Alosetron*[69, 86]	Ischem. colitis (IsC) Severe constip.(SC)	2000	1999 2000	RCT	IsC:l 1/324 vs 0/323[69] Constipation: 30% vs 3%	X	X	PR
Astemizole[42]	Fatal arrhythmia	1999	1999	Cohort/Case-Control	Ventricular arrhythmia RR = 19.0 (95%CI 4,8-76.0)[51[42]			PR
Fenfluramine[39, 40]	Heart valve disease	1997	1997	Cohort	Valvular surgery 5/24[39]			PR
Flosequinan[38, 87]	Cardiovascular events	1993	1993	RCT SE	Death RR = 1.41 P =< 0.001[87]		X	PR
Encenaide[51, 88]	Cardiovascular events	1991	1989	RCT SE	Death RR 3.6; (95% CI 1.7 to 8.5)[51]		X	PR

*RCT SE = randomized clinical trial stopped early
** ΔQTc = change in QT interval
S = Surrogate
PR = Patient Relevant
TdP: Torsade de Pointe
MI: Myocardial Infarction

LCL: lower limit of the one-sided 95% confidence interval
AOR: Adjusted Odds Ratio

IRR: Incidence Rate Ratio
HZ: Hazard Ratio
RR: Relative Risk

Analysis of the use of Comparative Studies to Justify the Withdrawals according to the GRADE Framework

- 15 withdrawals used comparative study design
  - 10 DsWSR used RCTs (9 RCTs used alone)
    - 8 RCTs used placebo as comparator
  - 4 DsWSR used Cohort studies (1 Cohort used alone)
  - 3 DsWSR used Case-controlled (2 Case-controlled used alone)
  - 12 DsWSR used patients' relevant outcomes/ 3 used surrogate outcomes with CRs
  - The magnitude of the effect tend to be higher in cohort studies and case-controlled studies compared to RCTs
  - Notion of replication were available only in 4 withdrawals

Tank You For Listening

Questions ?