

Testimony of David Graham
Before the House Committee on Energy and Commerce
Subcommittee on Oversight and Investigations
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Chairman Stupak and members of the subcommittee, thank you for the opportunity to speak about a subject of vital importance to the health of all Americans. My name is David Graham and I am currently the Associate Director for Science and Medicine in FDA's Office of Surveillance and Epidemiology (OSE). For more than 20 years, I have worked as an FDA physician-epidemiologist concerned with post-marketing drug safety. The statements I make today are my own. I do not represent the FDA's official view.

FDA's handling of Ketek is one more example that illustrates FDA is more concerned with serving the interests of industry than it is in patient safety. FDA ignored safety concerns raised by its own advisory committee, lied to that committee by withholding from it that a crucial clinical trial was fraudulent. Subsequently, FDA betrayed the American people when it lied to them, issuing a Public Health Advisory that referenced this same fraudulent study as proof of Ketek's safety. FDA scientists were threatened, intimidated, suppressed, transferred, and ultimately compelled to leave the Agency. OSE, ostensibly responsible for postmarketing safety issues, was relegated to the role of back seat "consultant," with no power or authority to intervene. CDER used postmarketing case reports from Europe and Latin America instead of a clinical trial to declare that Ketek is safe. I cannot think of a single other example where FDA used such data as the primary basis for approval of a drug's safety. OSE was not consulted about this unprecedented misuse of postmarketing data and would never have approved it. Ketek confirms that a national crisis in drug safety remains.

In November 2004, I testified before the Senate Finance Committee that FDA's handling of Vioxx was "a profound regulatory failure," and that "FDA, as currently configured, is incapable of protecting America against another Vioxx." I am here today to tell you that despite much hand waving by FDA, our nation is still at risk.

Vioxx was an enormous national catastrophe. Up to 60,000 Americans, most over the age of 50, died from Vioxx-related heart attacks, about as many as the number of US soldiers killed during the Viet Nam War. Another 80,000 suffered non-fatal, but nonetheless life-threatening, heart attacks. FDA had multiple opportunities to prevent this harm but did nothing. To this day, FDA denies that it made any mistakes and FDA was never held accountable for failing to place patient safety ahead of corporate profits. FDA is still an Agency in denial and remains incapable of reforming itself. I've included a table showing the estimated number of patients by State who were harmed or

killed by Vioxx-associated heart attacks. Every Congressional district in the US was affected by FDA's failure to put patients first. It is also important to recognize that Vioxx and Ketek aren't the only examples of FDA's chronic disregard for patient safety. FDA's failure has resulted in substantial patient harm from many other drugs as well, including Propulsid, acetaminophen (the active ingredient in Tylenol), SSRI antidepressants, antipsychotic medications, Lotronex, and Accutane to name just a few.

When it comes to drug safety, what's wrong with the FDA? In my view, there are four broad areas of FDA malfunction, which guarantee that such disasters will continue in the future unless decisive steps are taken now. These areas are 1) organizational structure; 2) organizational culture; 3) the misuse and abuse of science; and 4) suppression and intimidation of scientific staff. Time does not permit a comprehensive discussion of each of these.

The most important relates to organizational structure. CDER's primary mission is to review and approve new drugs. Within CDER, the Office of New Drugs (OND) has this responsibility. Post-approval, OND continues to have regulatory authority for all postmarketing safety issues that arise. This represents an inherent conflict of interest because the people who approve new drugs and certify that they are safe and effective are the same people who will decide if a postmarketing safety issue is important and if anything needs to be done about it. History shows that CDER and OND's predictable response to a new safety concern is to deny there is a problem, to suppress and threaten OSE and others who raise concern or press for action, and to procrastinate while patients die and company sales increase. Within CDER, there are no internal checks and balances, there is no separation of regulatory decision-making, authority, and responsibility, and ultimately, there is no accountability. Indeed, a senior CDER manager, speaking about Ketek, stated, "We're the FDA. No one can second guess us."

This organizational weakness is amplified by a massive imbalance in resources within CDER. OND has about 750 FTEs compared to about 130 in OSE. However, the imbalance is even greater because there are other Offices within CDER that have a major role in the final approval of a new drug. When these are considered, about 1200 people, roughly 90% of CDER, are focused on review and approval of new drugs. These numbers confirm that postmarketing safety is not a CDER priority. When safety issues arise, CDER management preferentially supports the perspective of this 90%.

CDER's culture regards industry as the primary client or customer. With PDUFA, CDER has increasingly aligned itself with the interests of the industry it is supposed to regulate. Even when lives hang in the balance, FDA takes its cue from industry. FDA officials insist that no new regulatory authorities are needed. That's simply not true.

New and explicit powers and authority are needed. Without them, FDA will continue to hide from its public responsibility and patients will pay the price.

In the wake of Vioxx, the Institute of Medicine was asked to review the way FDA handles drug safety. The IOM report, issued late last year, confirmed the substance of my November 2004 testimony. Here are a few quotes and paraphrases from that report.

“CDER is an organization in urgent need of great change...the Center’s organizational problems affect its ability to accomplish the mission of protecting and advancing the public’s health.”

PDUFA has “increased the Agency’s dependence on industry funding,” and “severely skewed the Agency’s attention to facilitating review and approval” of drugs.

The Committee was especially “concerned” that the “authority of postmarketing is solely in the hands of those who approve the drug” and “safety activities appear to be secondary or subservient to pre-market review and approval of drugs for marketing.” The Committee added that “the imbalance in formal role and authority between the review (OND) and surveillance/epidemiology (ODS/OSE) staff denotes subservience of the safety function, and along with that, a management devaluation of the latter discipline and approach.” Finally, the IOM Committee concluded that CDER is biased toward drug approval, and will not revise its regulatory approach to an already-approved drug

The Committee was extremely skeptical of the Agency’s recent efforts at reform, asserting they were nothing more than “moving boxes around on a chart.”

Does FDA’s response address the IOM’s most important concerns? I don’t have four hours to explain how superficial it is. But an article from the *New York Times*, written the day after FDA announced its response, says it all. Alan Goldhammer, deputy vice president with PhARMA, the major lobbying group for the pharmaceutical industry, praised the FDA response as being “very thoughtful and comprehensive” and added “the Agency has made...significant progress in improving and enhancing the drug safety system in the US.” Alta Charo, a professor of law and bioethics at the University of Wisconsin and a member of the IOM Committee that wrote the IOM report was “disappointed” that the agency had failed to give greater authority to OSE, which assesses the safety of drugs after they go on the market. She said, “We viewed that as critical.” So there you have it. Industry is pleased because nothing is really changed; OND controls postmarketing safety and OSE doesn’t. The public suffers because the foundational reform needed to protect them has been conspicuously avoided.

Finally, although this is not a legislative hearing, I am compelled by conscience to make the following comments. Vioxx is the main reason why legislation to reform FDA is being considered. The litmus test by which

any potential legislation is judged should be whether it would have prevented the Vioxx disaster, with the loss of 60,000 lives, from occurring. If it fails this test, you've done nothing more than "fiddle while Rome burns."

FDA's response to the IOM report, even if fully implemented, would not have prevented a single Vioxx heart attack or death. It also would not have protected anyone against Ketek or any of the other drugs I mentioned earlier. The Vioxx debacle was not due to a failure of surveillance, or a failure of resources. It was due to a failure of institutional decision-making. Unless the OSE and the postmarketing safety activities of FDA are separated from the OND, and given independent regulatory authority over the postmarketing portion of a drug's life cycle, all the money and databases in the world won't change the end result.

Similarly, had the proposed Kennedy-Enzi bill been in place when Vioxx came to market, not a single life would have been saved. This bill also would have had no effect on the way Ketek or the SSRI antidepressant issues unfolded. Why? The bill does not correct the root cause of FDA's failure to protect the public health. FDA's failure with Vioxx and the other mentioned drugs was a failure of institutional decision-making and, the organizational structure giving rise to this failure has been left unchanged. Kennedy-Enzi leaves OND in charge of postmarketing drug safety. Unless this is changed, we should expect more Vioxxes, more Keteks and more SSRI disasters. Sadly, Kennedy-Enzi is not fundamental FDA reform; it is fundamentally the status quo.

The Dodd-Grassley bill would create a separate Center for Postmarketing within FDA and would empower this Center with explicit authority to protect the public from unsafe medicines. This bill also frees postmarketing from the corrupting influence of PDUFA. Had this bill been in place prior to Vioxx, most of the 140,000 Vioxx-related heart attack deaths and injuries would have been prevented. Likewise, the handling of Ketek and the other drugs I mentioned would have been substantially different, with a substantial reduction in needless patient injury and death.

Thank you for your consideration of this critical subject and for the opportunity to address you today.

Table. Estimated excess number of fatal, non-fatal, and total acute myocardial infarctions (heart attacks) attributable to US Vioxx use.

	<u>State</u>	<u>Fatal</u> <u>heart attacks</u>	<u>Non-fatal</u> <u>heart attacks</u>	<u>Total</u>
1.	AK	133	176	309
2.	AL	926	1232	2158
3.	AR	568	756	1324
4.	AZ	1074	1428	2502
5.	CA	7116	9464	16580
6.	CO	905	1204	2109
7.	CT	716	952	1668
8.	DC	120	160	280
9.	DE	164	218	383
10.	FL	3368	4480	7848
11.	GA	1726	2296	4022
12.	HI	253	336	589
13.	IA	611	812	1423
14.	ID	274	364	638
15.	IL	2611	3472	6083
16.	IN	1284	1708	2992
17.	KS	568	756	1324
18.	KY	842	1120	1962
19.	LA	947	1260	2207
20.	MA	1326	1764	3090
21.	MD	1116	1484	2600
22.	ME	274	364	638
23.	MI	2084	2772	4856
24.	MN	1032	1372	2404
25.	MO	1179	1568	2747
26.	MS	589	784	1373
27.	MT	189	252	441
28.	NC	1684	2240	3924
29.	ND	135	179	314
30.	NE	358	476	834
31.	NH	253	336	589
32.	NJ	1768	2352	4120
33.	NM	379	504	883
34.	NV	421	560	981
35.	NY	4000	5320	9320
36.	OH	2400	3192	5592
37.	OK	737	980	1717
38.	OR	716	952	1668
39.	PA	2589	3444	6033
40.	RI	211	280	491
41.	SC	842	1120	1962
42.	SD	158	210	368
43.	TN	1200	1596	2796
44.	TX	4400	5852	10252
45.	UT	463	616	1079
46.	VA	1495	1988	3483
47.	VT	128	171	299
48.	WA	1242	1652	2894
49.	WI	1137	1512	2649
50.	WV	379	504	883
51.	WY	103	137	240