Vioxx FDA

The FDA Exposed: An Interview With Dr. David Graham, the Vioxx Whistleblower

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The following interview with Dr. David Graham (senior drug safety researcher at the FDA) was conducted by Manette Loudon, the lead investigator for Dr. Gary Null. This interview contains jaw-dropping insights about the corruption and crimes that take place every day inside the Food and Drug Administration. This is no outside critic, either: these are the words from a top FDA employee who has worked at the agency for two decades. If you've ever wondered how the drug industry could pull off the greatest con of our time -- and turn the human body into a profit-generating machine -- you're about to learn the shocking answers in this interview.

This interview is reprinted here with permission from Dr. Gary Null. Parts of this interview also appear in Dr. Gary Null's *Prescription For Disaster* video documentary, which is available at the Gary Null website and is a must-see video for anyone who wants to know the truth about thepharmaceutical industry and the FDA.

MANETTE: Dr. Graham, it's truly a pleasure to have the opportunity to interview you. Let me begin by asking you how long you've been with the FDA and what your current position is?

DR. GRAHAM: I've been with the FDA for 20 years. I'm currently the Associate Director for Science and Medicine in the Office of Drug Safety. That's my official job. But when I'm here today I'm speaking in my private capacity on my own time, and I do not represent the FDA. We can be pretty certain that the FDA would not agree with most of what I have to say. So with those disclaimers you know everything is okay.

MANETTE: On November 23, 2004 PBS Online News Hour Program you were quoted as making the following statement. “I would argue that the FDA as currently configured is incapable of protecting America against another Vioxx. Simply put, FDA and the Center for Drug Evaluation Research (CDER) are broken.” Since you've

made that statement, has anything changed within the FDA to fix what's broken and, if not, how serious is the problem that we're dealing with here?

DR. GRAHAM: Since November, when I appeared before the Senate Finance Committee and announced to the world that the FDA was incapable of protecting America from unsafe drugs or from another Vioxx, very little has changed on the surface and substantively nothing has changed. The structural problems that exist within the FDA, where the people who approve the drugs are also the ones who oversee the post marketing regulation of the drug, remain unchanged. The people who approve a drug when they see that there is a safety problem with it are very reluctant to do anything about it because it will reflect badly on them. They continue to let the damage occur. America is just as at risk now, as it was in November, as it was two years ago, and as it was five years ago.

MANETTE: In that same PBS program, you were also quoted saying, "The organizational structure within the CDER is currently geared towards the review and approval of new drugs. When a serious safety issue arises at post marketing, the immediate reaction is almost always one of denial, rejection and heat. They approved the drugs, so there can't possibly be anything wrong with it. This is an inherent conflict of interest." Based on what you're saying it appears that the FDA is responsible for protecting the interests of pharmaceutical companies and not the American people. Do you believe the FDA can protect the public from dangerous drugs?

DR. GRAHAM: As currently configured, the FDA is not able to adequately protect the American public. It's more interested in protecting the interests of industry. It views industry as its client, and the client is someone whose interest you represent. Unfortunately, that is the way the FDA is currently structured. Within the Center for Drug Evaluation and Research about 80 percent of the resources are geared towards the approval of new drugs and 20 percent is for everything else. Drug safety is about five percent. The "gorilla in the living room" is new drugs and approval. Congress has not only created that structure, they have also worsened that structure through the PDUFA, the Prescription Drug User Fee Act, by which drug companies pay money to the FDA so they will review and approve its drug. So you have that conflict as well.

MANETTE: When did that go into effect?

DR. GRAHAM: The Prescription Drug User Fee Act came into play in 1992. It was passed by Congress as a way of providing the FDA with more funds so that it could hire more physicians and other scientists to review drug applications so that drugs would be approved more quickly. For industry, every day a drug is held up from being marketed, represents a loss of one to two million dollars of profit. The incentive is to

review and approve the drugs as quickly as possible, and not stand in the way of profit-making. The FDA cooperates with that mandate.

MANETTE: And what about those new drugs? Are they any better than what already exists on the market?

DR. GRAHAM: It's a myth that is promulgated not only by industry but also by the FDA itself. It's a misperception that our lawmakers in Congress have as well and they've been fed this line by industry. Industry is saying there are all these lifesaving drugs that the FDA is slow to approve and people are dying in the streets because of it. The fact is that probably about two-thirds to three-quarters of the drugs that the FDA reviews are already on the market and are being reviewed for another indication. So, for example, if I've got a drug that can treat bronchitis and now it's going to be used to treat a urinary tract infection well, that's a new indication. But it's the same drug and we already know about the safety of the drug. There is nothing lifesaving there. There is nothing new. There is nothing innovative. A very small proportion of drugs represent a new drug that hasn't been marketed before. Most of those drugs are no better than the ones that exist. If you want to talk about breakthrough drugs – the ones that really make a difference in patients' lives and represent a revolution in pharmacology – we're talking about maybe one or two drugs a year. Most of them aren't breakthroughs and most of them aren't lifesaving, but they get treated as if they were.

MANETTE: Are you at liberty to discuss some of the problems your colleagues are finding with other drugs and if so, how widespread is the problem?

DR. GRAHAM: I'm really not at liberty to talk about things that pertain to my official duties at the FDA. I can talk in my private capacity, but I can't talk about material that would be confidential. What I can say is that there are a number of other scientists within the FDA who have also worked with drugs that they know are not safe, even though the FDA has approved or allowed them to remain on the market. They face some of the same difficulties that I do. The difference is that either the problem isn't as serious in terms of the numbers of people that were injured or that it's a fatal reaction – they're not willing to expose themselves to retaliation by the FDA - and retaliation would surely follow.

MANETTE: Do you think we should have any confidence in the FDA and if so, can you elaborate on what they do that you feel benefits the American people?

DR. GRAHAM: In terms of confidence in what the FDA does, there are two things that the FDA determines when it looks at a drug: it determines whether or not a drug is safe and it determines whether or not it's effective. Regarding the determination of

drug effectiveness, I think the FDA does a pretty good job. If the FDA says that the drug will have a particular effect, probably for many of the patients who take the drug it will actually have that effect. If the FDA says a given drug will lower blood pressure and you're somebody who has high blood pressure, there's a good chance that the drug will have an effect that lowers your blood pressure. That has to do with the rigor with which they force the drug companies to establish that the drug actually has an effect.

On the safety side, I think that the American public can't be very confident. They can have some confidence because it turns out that most drugs are remarkably safe. But, when there are unsafe drugs, the FDA is very likely to err on the side of industry. Rarely will they keep a drug from being marketed or pull a drug off the market. A lot of this has to do with the standards that the FDA uses for safety. When they look at efficacy, they assume that the drug doesn't work and the company has to prove that the drug does work. When they look at safety it's entirely the opposite. The FDA assumes the drug is safe and now it's up to the company to prove that the drug isn't safe. Well, that's a no-brainer. What company on earth is going to try to prove that the drug isn't safe? There's no incentive for the companies to do things right. The clinical trials that are done are too small, and as a result it's very unusual to find a serious safety problem in these clinical trials. Safety flaws are discovered after the drug gets on the market.

MANETTE: I read somewhere that a drug only has to be better than a sugar pill

DR. GRAHAM: Right. The standard that the FDA uses to approve a drug is primarily "does the drug work?" That's what they call efficacy. Most often, they'll compare the drug against something called a placebo or a sugar pill. It's basically something that doesn't have a medical effect. The assumption is that the drug will be no different than the sugar pill. The FDA puts the onus on the drug company to conduct a clinical trial to show that the drug is different from a sugar pill. The way the FDA's approval standards are, the drug does not necessarily have to have a very great effect in order to be approved. The drug might lower your blood pressure by just a few millimeters of mercury, but the FDA will say we can approve it because it does lower your blood pressure.

Now, would that be a benefit or are there other drugs out there – many other drugs – that patients could take instead that would lower their blood pressure by 10 or 15 or 20 millimeters? The FDA doesn't really care about that. What happens is the drug gets marketed. You've got two drugs that are out there – one drug that effectively lowers your blood pressure a substantial degree and another drug that barely lowers your blood pressure at all. The company that has that second drug markets it like it's this breakthrough medicine. It lowers your blood pressure and they have all these glitzy

ads, direct-to-consumer advertising. Lots of patients and lots of doctors will use that medication. What happens in the process is these patients are actually in a sense being denied a more effective treatment because the FDA doesn't require that drugs that come on to market be at least equivalent to, or better than, the drugs that are already there. All they have to do is be better than a sugar pill.

MANETTE: When you consider the financial impact your whistle blowing has had on the pharmaceutical industry do you have any fears that your life may be in jeopardy?

DR. GRAHAM: I have tried not to think about that. In the work that I've done I've never really thought about what the financial impact would be on any particular company. I put that out of my mind because my primary concern is whether or not the drug is safe. If it's not safe, how unsafe is it and how many people are being hurt by it? In terms of when I identify an unsafe drug, to me it doesn't really matter what drug company it is. I've helped to get ten different drugs off the market, and they're from ten different drug companies. It's not a vendetta against any particular drug company. I have to hope that the drug companies don't take it personally. I'm just a scientist doing my job and I have to leave the rest to God to protect me.

MANETTE: Has anyone tried to silence you and stop you from becoming a whistleblower?

DR. GRAHAM: Prior to my Senate testimony in mid-November of 2004, there was an orchestrated campaign by senior level FDA managers to intimidate me so that I would not testify before Congress. This intimidation took several forms. One attack came from our acting Center Director who contacted the editor of the Lancet, the prestigious medical journal in the United Kingdom, and intimated to the editor that I had committed scientific misconduct and that they shouldn't publish a paper that I had written showing that Vioxx increases the risks of heart attack. This high-level FDA official never talked to me about this allegation. He just went directly to the Lancet.

The second attack was from other high level FDA officials who contacted Senator Grassley's office and attempted to prevent Senator Grassley and his staff from supporting me and calling me as a witness. They knew that if they could disarm Senator Grassley that would neutralize me.

The third attack came from senior FDA officials who contacted Tom Devine, my attorney at the Government Accountability Project, and attempted to convince him that he should not represent me because I was guilty of scientific misconduct; I was a bully; a demigod; and a terrible person that couldn't be trusted. These people were posing as whistleblowers themselves ratting on another whistleblower. Some of these

senior level FDA officials were in my supervisory chain and are people I work for. They were involved in a coordinated attempt to discredit me and to smear my name and to prevent me from giving testimony.

There's one other thing that happened the week before I testified. The Acting Commissioner of the FDA invited me to his office and offered me a job in the Commissioner's Office to oversee the revitalization of drug safety for the FDA if I would just leave the Office of Drug Safety and come to the Commissioner's Office. Obviously he had been tipped off by people in the Senate Finance Committee who are sympathetic to the FDA's status quo that I was going to be called as a witness. To preempt that, he offers me this job, which basically would have been exile to a fancy title with no real ability to have an impact. This was a conspiracy and it was coordinated and there was collaboration among senior level FDA officials. What a mess!

MANETTE: All of these attacks backfired on them. Tell us a little bit about that.

DR. GRAHAM: Well, Senator Grassley and his staff quickly realized that what they were saying about me was fabricated. The editor of The Lancet also realized that what the high level FDA officials were saying to him was a pack of lies. He sent emails to them saying it looked to him as if they were trying to interfere with his editorial process. He was very savvy to what these people were doing. Tom Devine, as he said publicly, was very interested in doing the right thing. He said, "We don't want to protect somebody who's a lawbreaker and who really isn't representing the truth so produce your evidence." They had no evidence because there is no evidence. But I produced my evidence. I showed him all the documentation, all the emails, and the reports that I've written. They flunked every test and I passed every test.

In all of the criticism I have received relating to Vioxx and drug safety, they've never attacked the work or the science that I've done or the results that I've come to. What they've done is call me names. The ad hominem attack is the last refuge of the indefensible. They don't have an argument that's substantial. They know that they're vulnerable. They know that they've disserved the American people. The FDA is responsible for 140,000 heart attacks and 60,000 dead Americans. That's as many people as were killed in the Vietnam War. Yet the FDA points the finger at me and says, "Well, this guy's a rat, you can't trust him," but nobody is calling them to account. Congress isn't calling them to account. For the American people, it's dropped off the radar screen. They should be screaming because this can happen again.

MANETTE: On CNN with Lou Dobbs you said that there was a certain "culture" that exists at the FDA. Can you explain what you meant by that?

DR. GRAHAM: The FDA has a very peculiar culture. It runs like the army so it's very hierarchal. You have to go through the chain of command and if somebody up above you says that they want things done in a particular way well, they want it done in a particular way. The culture also views industry as the client.

They're serving industry rather than the public. In fact, when a former office director for the Office of Drug Safety criticized me and tried to get me to change a report I'd written on another drug – Arava – he said to me and to a colleague who was a coauthor on this report that "industry is our client." I begged to differ with him. I said, "No, industry is not the client, it's the American people, the people who pay our taxes. That's who we're here to serve." He said, "No! Industry is our client." I ended the conversation by saying, "Well, industry may be your client, but it will never be my client."

Another aspect to the culture at the FDA is that it overvalues the benefits of drugs and undervalues the risks of drugs. And so the FDA will always say to you, "Well, we're leaving this drug on the market because the benefits exceed the risks." Well, the FDA has never assessed the benefit of any drug that it's ever approved. It works on what's called efficacy. Does the drug work or not? Does it lower your blood pressure or does it lower your blood sugar? Not: Does it prolong your life? Does it prevent you from having a heart attack? Those are benefits. All they focus on is efficacy.

For example, ask the FDA why on earth they didn't ban high dose Vioxx after the VIGOR Study showed in early 2000 that it increased the risk of heart attack by 500 percent? High dose Vioxx was approved for the short-term treatment of acute pain. What earthly benefit was there that exceeds a 500 percent increase in heart attack risk? Ask the FDA to produce its benefit analysis that shows that the benefits exceed the risks. It doesn't exist. The FDA has never looked at benefit. The FDA just says to the American people, "The benefits exceed the risks. Trust me. Believe me." If you held the FDA to its proof the American people would see how badly served they've been by the FDA and its culture that belittles safety in the drug companies' interest.

If the FDA were to pull a drug due to safety issues, it would hurt the marketing of the drug. It might also call into question why they approved the drug in the first place. Therefore, you get this culture of cover-up, this culture of suppression, this culture of denial, and this culture that demonstrates above all else that industry is the client and not the American people.

MANETTE: Have your peers turned against you?

DR. GRAHAM: No. I've been very fortunate. Tom Devine at GAP has told me that the experience of a typical whistleblower is that they'll have the support of their peers

but the peers will be so afraid of retaliation that they won't express that support in public. I've had a very different experience. I've been basically embraced by my peers as someone who has said what they want to say and what they wished they had been able to say and that they recognize as the truth. They're really proud of the fact that I've said it and they're not afraid to be seen with me. They're not afraid to work with me. I've been pretty fortunate in that way.

Now with management it's been another story. Upper management avoids me and doesn't talk to me. I could be walking down the hall and I'll say hello, and they'll act like I'm not there. They don't give me interesting work assignments. They don't call me in to consult on things that I should be consulted on even though I am the senior epidemiologist in the Office of Drug Safety with more experience than any of the other people there. I'm looked up to by the scientific staff because of that expertise. Basically, I feel like I'm in the Gulag.

MANETTE: How do you cope with that going to work each day?

DR. GRAHAM: It's difficult. It's a mind game. They're hoping that I'll just become very frustrated and disillusioned and leave or that I'll slip up in some way so that they can take some sort of action against me. As Tom Devine at GAP has said, I have to be Saint David. I can't afford to make any mistakes. That's very difficult and it is a little bit discouraging. But I've been a target of retaliation in the past. You take ten drugs off the market well, no good deed goes unpunished at the FDA. I've experienced retaliation with many of those other episodes but not as severe as what I've experienced with Vioxx. This is the first time that my job was actually in jeopardy and where the FDA actually intended to fire me. That was stopped only because Senator Grassley intervened. He put the heat on the FDA and told them, "Lay off. This guy has told the truth. He's helped America. Whose side are you on?"

MANETTE: Were there any warnings that Vioxx was a problem? Did you see the disaster coming?

DR. GRAHAM: I think that I was afraid that there would be a disaster, but I only became aware of this with the publication of the VIGOR Study, which was this large clinical trial that was done that showed that Vioxx increased the risk of heart attack five fold. That study was published in November of 2000. It was written, performed, and paid for by industry. What industry concluded was not that Vioxx increases the risks of heart attack, but that the drug they were comparing it against – Naproxen – decreased the risk of heart attack. I knew that was not a sustainable argument. There was no way that Naproxen was that protective against heart attacks. Clearly Vioxx was the problem. I knew that Vioxx was on the road to becoming a blockbuster drug (20 million users). All the ingredients were there for a disaster.

The FDA is responsible in so far as it could have prevented much of the damage, heart attacks, and deaths simply by banning the high dose Vioxx back in mid 2000 when they knew the results of the VIGOR Study. But the FDA did nothing for almost two years. They were "negotiating" with the company over a label. What did the label accomplish? Nothing! Before the label 17 or 18 percent of people who took Vioxx took the high dose. After the label change 17 or 18 percent were still taking the high dose. High dose use didn't change at all. People didn't read the label, and if they read the label they wouldn't know what to do anyway because it was very confusing. The right thing to do would have been to pull the high dose off the market because there is no benefit for short-term relief of acute pain that exceeds this risk. The FDA made bad decisions based on its culture and its institutionalized biases that favor industry, and as a result thousands of Americans died. Americans and Congress should be screaming bloody murder. They should be beating on the doors of the FDA demanding change.

MANETTE: It's estimated that over 200,000 people a year die from prescription drugs. Do you see this as a serious problem and do you think many of these treatments are more dangerous than the disease itself?

DR. GRAHAM: Death from adverse drug reactions is one of the leading causes of death in the United States. It turns out that most of these adverse reactions are actually what are expected in the sense that they are an extension of the drug's action. For example, we know that drugs for diabetes can lower your blood sugar. If you're more sensitive to the drug than the normal person and it lowers your blood sugar too much, causing you to have a seizure while driving your car and you get killed, well, you died from an adverse drug reaction, but it wasn't something unexpected.

The blood thinner Coumadin is another example. That drug provides a benefit, but it is also responsible for probably more deaths than any single drug currently marketed. But it has a recognized benefit and there aren't other drugs to do what it does or to do what it does well. So physiciansaccept that there are patients who are in a serious situation and who might die without the drug, so they take it.

Yes, drugs cause a lot of harm. Unfortunately, we haven't quantified the benefits. For most of these drugs it's more belief. It's faith. We have faith that they'll confer a benefit, but the FDA hasn't demonstrated that they confer a benefit. We're getting much better at quantitating the risks. In the future what we need to do is just take the risks and look hard and dispassionately at what the real benefits are. If the benefits aren't there we shouldn't be having discussions about labeling the drug. You need to weed the garden patch of drugs that aren't doing what they're supposed to do. The FDA has not been very good about that; it likes to cultivate all these weeds.

MANETTE: In a perfect world what role do you see the FDA playing in our nation's health?

DR. GRAHAM: In a perfect world, I think the FDA would need to be restructured. If it were restructured properly, I think that it could actually provide a great benefit to the public health. I would recommend several changes. First, I would separate safety and post-marketing from the pre-marketing. I would create a separate center for product safety. Actually, Senator Grassley and Dodd have recently introduced legislation to create an independent center for post-marketing safety that would serve to protect the American people from unsafe drugs. This isn't happening now.

On the pre-marketing side, the FDA needs to pay greater attention to safety. They need to have larger clinical trials. They need to compare drug products against other drugs that treat the same indication rather than comparing a drug against a sugar pill. What we want in the end are drugs that actually have better benefit.

The FDA also needs to determine the post-marketing benefits of a drug. I've done that for several drugs. How many people are actually benefiting? How many people are living longer versus those who are having their lives shortened? Only when you have that kind of information can you make rational decisions about a medication. The times when I've done the benefit analysis, I've been chastised, criticized and suppressed by the FDA. These benefit analyses should be done as a matter of routine.

There is a lot that the FDA could do to improve, but the changes aren't going to happen on their own. Congress is going to have to make them happen. There's an expression, “the zebra doesn't change its stripes nor the leopard its spots.” The FDA isn't going to change the way it does business; changes will have to be imposed from outside.

MANETTE: How you do feel about direct-to-consumer advertising?

DR. GRAHAM: Direct-to-consumer advertising in general is a great disservice to the American people. We see wonderful ads of people demonstrating their health, whether they're skating across the ice or doing their Tai chi. Madison Avenue knows that a picture is worth a thousand words, so they convey an image, a message, and it makes an impression on patients and on physicians. It creates needs or desires where there really isn't a need or a desire.

There was a recent study in The Journal of The American Medical Association that showed that if patients mentioned a drug that they've seen on television to their physician they were much more likely to be prescribed that drug by the doctor. Drug

companies know this. That's why they do it. Would the Vioxx disaster have been as great and as large in the absence of direct-to-consumer advertising? I submit that the numbers would have been far lower than what they were. Direct-to-consumer advertising is part of what made Vioxx a blockbuster drug. It helped to rev the market up to get people to want to use the drug.

Clearly, direct-to-consumer advertising does not serve the American people well. Madison Avenue is smarter than the most intelligent American. That's why they make so much money and that's why the drug companies go to them to sell their products. We're not living in a neutral world where the information we're getting is objective and unbiased. It might be that the average American, given all the data, all the facts, and all the information in an objective way could make an intelligent, rational decision. But we don't live in that kind of world. We live in a world where what we're seeing is a visual image of these people being vital and healthy and cured of their illnesses. And it's all because of this little pill that they're taking. A patient with that condition says, "I want to be just like that person." So they go to the doctor and say, "I want that pill." Are their lives changed? Maybe some people's lives are changed, but I think most aren't.

MANETTE: What do you think people hear when they're watching the ad and after the ad they list all the possible side effects?

DR. GRAHAM: I don't think it registers. You have the visual image that conveys one message. Then you have the voice that's speaking over this pictorial being shown telling you what this drug is good for. Then at the end the auctioneer gets on and says, "You know this drug could cause…," and they rattle off 25 different things in three seconds. You're lucky if you hear anything. I don't think that people come away with it and they certainly don't come away with any sense of how likely it is to happen because the visual image overpowers anything that gets said.

It's the same with the ads that appear in magazines. Companies are required to put some of the labeling in the ad. You have the ad on the one side – that's the picture. It shows this person being healthy because they take this pill. The fine print is all on the next page. People aren't going to read the fine print. It's the same thing with labeling for physicians. Physicians don't read product labels. Where do they learn about drugs? They learn about drugs from the detail person from the drug company or from other colleagues who have used the drug. They're not learning it from the labeling.

MANETTE: Do you think there is a criminal cover-up going on between the FDA and Big Pharma to approve dangerous drugs that sicken and kill Americans?

DR. GRAHAM: I have no knowledge of criminal activity and I'm sure there are legal standards for what's criminal and what's not. I do think that there is an institutional bias at the FDA that says we will look for a way to say "yes" to the approval of any drug that comes down the pipe. If a drug is so bad that they can't find a reason to approve it, they won't. But, if there is any way that they can approve the drug, they will. The way this is done is by what's called the "indication." Why is it that you're going to take the drug? Maybe you're going to take it because you have high blood pressure. Maybe you'll take it because you have high cholesterol. That's the indication. A company may come in with a drug and want to get it approved for five different indications. One of them is a really insignificant indication that affects a very small number of people. The main indication might affect millions of people. The drug doesn't show efficacy for that major indication, but they're able to somehow or another approve the small indication.

So the drug gets approved for this narrow indication, but the FDA and the drug company both know that it's going to be used for that other indication. It's going to be used "off-label." Then, the FDA turns around and says that they don't regulate the "off- label" use of drugs. No. But, they aid and abet it. They allow it to happen and in many instances "off-label" use of a drug product is a public health threat. The FDA has a responsibility to protect the public health. The FDA should be intervening, but they don't. In my own experience I have seen multiple examples where I've heard people say, "We can't ask a company to put that in the labeling because the company will say no." Or, "We can't do that because that will decrease their marketing. We've got to try to approve this drug. Let's see if we can give them this small indication. At least it's giving them something. You've got to find a way to say yes."

That is the typical attitude of the FDA culture. I think Congress is partially responsible for that because when they issued the PDUFA, the Prescription Drug User Fee Act, what they were really saying was, "We want you to review these drug applications more quickly because you're keeping lifesaving medicines from the American people." That's the line they were fed by Big Pharma. So they pressure the FDA and the FDA gets the message. It's a really pernicious system. I think it's unfortunate. There are many people from the FDA who have examples that they unfortunately can't talk about. They'd lose their job and maybe get thrown in prison because you can't discuss confidential and trade secret information. But the fact is these things happen at the FDA and there have been multiple examples in the past where one could see evidence of that.

MANETTE: Did your faith as a devout Roman Catholic play any role in the decisions you made to put your career on the line to report the truth?

DR. GRAHAM: It did in so far as my faith forms my conscience. It's sort of my sense of what's right and what's wrong and what I am and am not responsible for. I was in a situation here with Vioxx where I was invited by Senator Grassley's office to testify. I could have told them no, but then they would have subpoenaed me. So of course I went peaceably. I was faced with this dilemma. Should I lay it on the line and tell them the way it really is or do I kind of downplay it? There are ways of doing that.

What I concluded was that I'm now being given the opportunity to tell the truth to the people who are in a position to actually make a difference. I can't make a difference. I can't change the FDA, but Congress can. If I don't tell them the truth, then I'm now responsible, in part, for future deaths. I don't want to become a co-conspirator with the FDA in what happens with Vioxx because tens of thousands of people were injured or killed because of the FDA's disregard for safety. If I keep quiet about that, now I'm part of the problem. I'm one of them, and at that point then my conscience asks me, "You know what the truth is, are you going to speak it or aren't you?"

So I went ahead and did that and prayed that it all works out well for me personally. That I have a job and I'll be able to support my family, that I'm protected from retaliation, that maybe some good will come out of that. My faith plays a role, but it wasn't a direct teaching of the church. You have to do x, y and z, but it's the faith as I've internalized it. My conscience is formed by the voice of Christ speaking internally to me. That's what the conscience is; it's the voice of God speaking to each and every one of us about what's right and what's wrong. I knew what was right. If I walked away from that nobody else would have to do anything. I'd be beating myself up because my conscience would condemn me. So yes, faith plays a part in every thing that I do. It's not saying I'm a saint, because I'm not. But I can't separate who I am from my religious faith. It's all part of the same person.

MANETTE: Do you think Congress genuinely wants to fix the problems at the FDA or are too many politicians influenced by the pharmaceutical industry?

DR. GRAHAM: I don't know what Congress will do in the end. My hope is that they will act decisively to reform the FDA and make the American people safer by having strong post-marketing. Will that happen or not? I don't know. I think there are many people in Congress who see this as a serious problem and who very much want to see a change. I think at the same time there are other people who don't think it's such a bad problem, and many of those people honestly believe that. For those people I'd say they haven't seen the evidence so they don't really understand how bad the problem is. There are undoubtedly some people who are influenced by industry. Does that influence their judgment in the end? I don't know. They'd probably say no, it doesn't. Maybe at a conscious level it doesn't. But we have the same phenomenon in the scientific world where we look atresearch studies that are funded by industry

and studies that are funded by government, by National Institutes of Health or the Medical Research Council in the United Kingdom. Multiple studies have been done that have shown that if your study is funded by industry you are much likelier – about five times more likely – to come up with the result that's favorable to the drug company than if your study on the same subject is funded by an independent body unrelated to the company.

Now, are the researchers who did this study biased? Are they consciously cheating and manipulating the data and everything else? No. I don't think that's happening at all, but the fact is if the study is funded by industry it's much more likely to be favorable to industry. Without attributing bad motivations to the scientists doing those studies all I can do is point to a strong correlation.

With Congress I would be concerned that there could be a strong correlation there because Pharma is very bright. They fund as many politicians as they can. They get to the Republicans and the Democrats. Look at the funding on the major committees, the Health, Education, Labor and Pension Committee in the Senate or the Oversight and Investigations Subcommittee in the House. The Wall Street Journal reported recently that many people on these committees are funded by industry to a substantial degree. Industry knows how to exercise influence. What we have to do is overcome that influence with evidence, and then rely on the fact that at the end of the day the Congress will do what's best for the American people.

Will that happen? I don't know because then it gets embroiled in politics. You know, Republicans versus Democrats, the left versus the right, conservatives versus liberals. Yet, what we're talking about is public health and public health is nonpartisan. I can say this with certainty. For every member of the House of Representatives somebody in their district died because of Vioxx. Somebody in their district had a heart attack because of Vioxx. For every Senator in the Senate, many more people in their state died because of Vioxx or had a heart attack because of Vioxx. It doesn't matter whether it's a red state or a blue state. Those are human beings and what we're talking about is public health. What I'm hoping is that Congress will respond. There is a problem and the evidence is overwhelming, but we'll just have to wait and see.

MANETTE: What are you thoughts on President Bush's attempt to pass tort reform, which would protect most pharmaceutical companies from lawsuits except in the most egregious cases?

DR. GRAHAM: I think it's dangerous and wrong for the following reasons. We already have an FDA that's been neutralized by industry and sees industry as its client. The Center for Drug Evaluation and The Office of New Drugs dominates drug safety so that the drug safety is not independent. Drug safety can't protect the American

people. So government now isn't going to protect the average citizen from the consequences of unsafe drugs. The only alternative they have left is the legal system – the tort system. It's not a wonderful system. It would be much better if we had effective post-marketing regulation so that we could get bad drugs off the market before they hurt more people, but that's been neutralized. All that's left to people now is the courts. That's the only way we have of getting companies to change their behavior.

What tort reform will do is remove that threat as well. It's basically giving companies immunity because now the people who are injured by the drugs can't recover damages that might actually mean something to industry. I mean $250,000 for damages; they blow that in one ad campaign. To them that's nothing. But a lawsuit for multiple millions of dollars has more of an impact. Now, is that optimal? No. But the fact is that since we have a regulatory agency that doesn't regulate and we have a public health agency that doesn't protect the public, we have thousands of people who are being injured by products that the FDA knows are unsafe. The FDA knew there was a problem with Vioxx. They knew it was a big problem back in mid 2000 yet did nothing about it.

There has to be a system in place that reins companies in. If the FDA isn't going to exercise control over companies, then who will? How will it happen? I don't think that working through the courts and lawsuits is a particularly effective way of doing it; but it's the only recourse we have now, and that will be removed as well. You can demonize the trial lawyers but I think that there are patients who are severely injured by drugs. The defense is, "It's on the labels so we're protected." The problem is that nobody reads the labels so how do they protect anyone? The FDA should be making those decisions.

MANETTE: What can you tell us about all the antidepressants on the market that millions of children are taking?

DR. GRAHAM: In early 2004, SSRI antidepressants and suicidal behavior was a big safety issue. The FDA had suppressed a report written by a colleague of mine in drug safety and had prevented him from presenting this information in an advisory committee meeting. That information leaked to the media, embarrassing the FDA because it had been caught suppressing very important information – that most of the antidepressants don't work for treating children. Someone in my supervisory chain initiated a criminal investigation to identify the person who had leaked this information to the media. It turns out that the investigation ordered by these FDA officials was illegal. They broke federal laws – at least two or three federal laws – in ordering this investigation.

I think it's well established that depression is very common in adolescence. With the antidepressants that we have on the market right now only one of them has been shown to work in children and that's Fluoxetine or Prozac. All the other SSRI antidepressants are no better than sugar pills. However, if you were to read the labeling for these drugs it doesn't point that fact out so patients think one SSRI is as good as another. This is another way that the FDA has betrayed the American public and has betrayed the public health.

With the SSRI and antidepressants what the FDA should have insisted on was a signed informed consent at the time a child was going to be treated. That informed consent would say three things. One, these are the antidepressants that are available. Only Fluoxetine has been shown to work for depression in children. All the other drugs are no better than placebo. That's point two. No better than placebos. No better than sugar pills. Third, all of these drugs appear to have the ability to increase the risk of suicidal behavior. As a parent, if I see that in writing and the psychiatrist or GP is going to write the prescription and put my child on some drug other than Fluoxetine, I can say, "Doc, why are you putting my child on a drug that doesn't work in kids."

The FDA didn't want patients to have that information so they refused to have signed informed consent. The companies didn't want the patients to have that information because all of a sudden the "off-label" use of these drugs would dry up. So whose interest was being served there?

MANETTE: How do you feel about taking the approval process out of the hands of the FDA?

DR. GRAHAM: Well, where would you put it? If you put it somewhere else they're going to eventually become co-opted the way the FDA has been co-opted. I think the most that we could probably hope for is to try to disassociate the industry pressures from the approval decision. You have to change the culture of the organization, and you have to change the incentives in the organization. The culture and the incentives that the FDA operates by would have to be changed, and Congress can do that through legislation and by establishing different standards for how a drug gets approved. Not only do you have to show that the drug is effective, but you've got to show that it works as well or better than other drugs that treat that indication. You've got to prove to me that the drug is safe, not that the drug is harmful because you're never going to prove to me that the drug is harmful. You set up stringent standards of evidence that might lead to the approval of safe drugs that actually have benefits to the population.

Then pair that up with an independent post marketing regulation. Currently, the pre-market people who approve the drug decide what happens after it's on the market. If the drug needs to come off the market, they're the ones who have to say yes at the end

of the day. The people at the FDA who approved the drug, the Office of New Drugs, they are the single greatest obstacle when it comes to removing unsafe drugs from the market. I can vouch for that from personal experience. What you have to do is you have to take that responsibility and power away from them and put it with the group who sees their mission as serving the public and protecting the public health from unsafe drugs. I think if you do those two things you'd be a long way towards getting the FDA on the right footing.

Also, it would probably be beneficial not to have the FDA's funding come from industry. He who pays the piper calls the tune, and we now have a captured agency. Industry underwrites more than 50 percent of the Center for Drug Evaluation's budget. When industry yanks the chain whose neck is going to get tugged? The Center for Drug Evaluation! If industry isn't happy with them and the funding dries up what are we going to do? We're going to have to let half our people go. The program is going to shrink. Congress is going to be jumping up and down on our back. So it's a captured agency and America is not well served when industry is calling all the shots. Yes, industry has a right to make a legitimate profit from marketing products that help the American people. But you shouldn't have a situation that just basically leaves the American public defenseless. And that's what we have right now. We're virtually defenseless.

MANETTE: Are there other Vioxx's out there? Do you think this will repeat itself at this high profile level?

DR. GRAHAM: At this current moment I don't think there are other drugs out there that are as bad as Vioxx in terms of the enormous numbers of people that were hurt. During my Senate testimony I did mention that there were five other drugs that I thought the FDA really needed to reevaluate because in my estimation the benefit to risk was misjudged. After I named those five drugs the FDA was in the media saying that I did junk science and that these drugs were safe and effective and that I was a crackpot. However, recently the FDA announced that they were going to take Bextra off the market. Well, Bextra was one of the five I mentioned. They announced that with Acutane they were going to impose a restricted distribution system. Well, I had recommended a restricted distribution system 15 years ago. The major problem with Acutane is that it's just so widely overused that it causes an enormous amount of potential harm to pregnancy exposure. If we restricted the use of the drug to the small number of women who really need it each year, the problem would be pretty much resolved. But the FDA didn't want to do that because it would interfere with company profits. If you restrict the distribution and only one-tenth of the people who are getting it now are getting it tomorrow, profit will drop 90 percent. Of course companies aren't going to go along with that and the FDA isn't going to do anything that's going to harm corporate profit.

After my Senate testimony the FDA announced that they can look at other drugs – not only the other three of the five that I mentioned. There are other drugs on the market that I prefer not to talk about that the FDA knows are killing people. Ten or 100 people a year are dying because of the use of a particular drug or being hospitalized. Hundreds or maybe thousands of people are being hospitalized each year. For some of those drugs the benefits do exceed the risks. For others, it's clear that more could and should be done and maybe that means restricting the distribution of the drug's use or maybe it means banning an indication for the drug saying the drug should not be used for particular indications. Maybe it would be something like with the SSRI's where I believe there should be signed informed consent so that parents will know that the drug the doctor is prescribing for their son or daughter actually doesn't work in children.

I think that there are many things that can be done that haven't been done. There are other unsafe drugs out there, and the nature of our business is that a drug could be approved tomorrow that turns out to be the next Vioxx and we won't know until it happens. Then the question is, how quickly do we identify the problem and how quickly do we take effective action against it? We're pretty good at identifying these problems quickly. Where the FDA falls flat on its face is that there is a long period of time in which it does nothing. Then what it normally does is woefully inadequate and ineffective and as a result the body count mounts and that needs to be changed. Maybe Congress will change that.

MANETTE: Let's talk about incentives. When you say incentives what do you mean? For example, working at the FDA, is their pay somehow based on how many drugs they approve?

DR. GRAHAM: Currently, the performance evaluations for managers at the FDA are built around the drug review. How many reviews did they get done? Did they meet their PDUFA deadlines? It looks bad if you miss your PDUFA deadlines. The unspoken mores – what's the expected – is that you're going to approve as many of these drugs as you can. There has to be an overwhelming reason for you not to approve. Frequently what will happen is that these medical officers in their review will recommend that a drug not be approved and they get overruled by the higher ups because the higher ups are answering to a different set of incentives. You have to change that. A lot of that comes from the leaders. What I want to see is does the drug really make a difference? Is it beneficial?

There are many classes of drugs where we've got 10 or 15 members of that class. They all lower your blood pressure. They all lower your cholesterol. Another one comes along and the FDA feels its obligation to approve it. Why? Maybe the standard should be that for the drugs that come later in a class, they've got to show that they're

actually better than the drugs on the market because we've already got these other drugs that work. That would create incentives maybe within industry to develop drugs that are better than the ones that are already there. Currently, the way the incentives are for industry, it's safer to do a "me too" drug, another drug in the same class.

MANETTE: Do you think that the FDA should not be partially funded by industry?

DR. GRAHAM: I think that PDUFA funding for the FDA is a mistake.

MANETTE: Can you explain that a little more clearly because most people don't know what PDUFA funding is?

DR. GRAHAM: The drug companies pay a substantial amount of money to the FDA at the time that they bring a drug application for approval in order for the FDA to review the drug. Basically it's a tax. It's a fee. Industry pays the fee, and the FDA will review the drug application. But the real expectation is from the company: "We've paid our money, now approve our drug." That's basically how the FDA reacts as well. I think that the funding for the FDA should be independent of the industry that it's regulating and I think in the scientific field there's good evidence to support this notion. Industry money is influencing the decisions that get made, and it creates this incentive structure. You have this culture, you have these expectations, you have pressure from Congress. All of them come to a head at the FDA and all of those incentives are in the direction of "approve the drug." That's what happens so I believe that the FDA is unduly influenced by industry and that undue influence is in part the result of industry money funding the FDA operations.

MANETTE: Dr. Graham, thank you for your commitment to your convictions and for sharing insights that drove you to save many lives.

DR. GRAHAM: You're welcome. I hope I've helped.