

David Ross on the FDA

By Norman M. Goldfarb

David Ross is a board-certified physician in internal medicine and infectious diseases. He holds a PhD in Biochemistry and MD from New York University School of Medicine, where he also did his internal medicine residency. He did an infectious disease fellowship at Yale, and later joined the faculty there as an instructor. He joined FDA in 1996 as a Medical Officer in the Division of Anti-infective Drug Products, which is now part of the Division of Anti-Infective and Ophthalmologic Products. During his 10 years at FDA, he was promoted to Medical Team Leader, Deputy Director of the Office of Drug Evaluation Six (which handled therapeutic biologics that had been transferred over from the Center for Biologics), and then Associate Director for Regulatory Science in the Office of Oncology. In 2006, he left FDA and joined the Department of Veterans Affairs as Director of Clinical Public Health Programs. He is also an active clinician at the Washington VA.

Given your education and training, you had lots of different options for a career. What appealed to you about the FDA?

The FDA was a great opportunity to make a difference in public health. Intellectually it was clearly an incredibly exciting opportunity. It was a different route than the traditional careers of focusing only on clinical medicine or only on laboratory-based research.

I am very glad that I spent 10 years with FDA. I worked with a phenomenal number of really good people. I also had very good interactions with physicians and scientists in the drug development community and pharmaceutical companies, which was a real treat. There are many phenomenally bright, hard-working, committed people in the pharmaceutical industry.

If a PhD or MD was considering joining the FDA now, what advice would you give them?

FDA is still a very interesting place. There is a lot of important and interesting work being done there. However, I'd say to go in with your eyes open. The Prescription Drug User Fee Act (PDUFA) of 1992 started changing the culture at FDA. In 1997, as part of the FDA Modernization Act, Congress explicitly changed the mission of FDA from assuring that marketed drugs are safe and effective to making sure that the American public has timely access to safe and effective drugs. Getting drugs out there quickly became the priority. Industry has become FDA's "client." In 1994 and onwards, Congress started screaming at FDA about holding up new drugs. Newt Gingrich called David Kessler, Commissioner of the FDA from 1990 to 1997, "the biggest thug in America." People at FDA are like anywhere else; they don't like being yelled at by powerful people. The message was: start doing what industry wants.

To put the change in perspective, over the last several months, FDA officials met five times with members of patient groups to discuss renewal of PDUFA, and over one hundred times with members of industry groups. People at FDA know they have to be careful about not upsetting industry.

Recently, an ad recruiting medical officers and scientists appeared in *Express*, a free newspaper in Washington DC. In the past, these ads have talked about helping public health through drug regulation. Now, they explicitly say your job will be to advance public health

through drug development. The FDA has become a drug development agency, rather than a drug regulation agency.

There are really two FDAs. There is the FDA of the people on the front lines who are doing the work, and there is the FDA of the managers who are maintaining the appearance that they are doing what they are supposed to be doing even if they really are not. Not all of them, of course. There is a huge divide between the front-line people and some of the managers.

FDA never admits it made a mistake. They never say, "We were wrong to present data to an advisory committee when we knew it was fraudulent." They never say, "We were wrong to interfere with the publication of a scientific paper." They always have a rationalization. That's the managers; it's not the people on the front lines. Whatever they want to do, they say, "This is in the best interest of public health." It is an amazing coincidence that the two always happen to line up. Industry and FDA have overlapping but different objectives. A lot of people at FDA somehow find a way of exactly aligning the two, but sometimes they just can't be aligned.

But I want to be very, very clear. We have the most innovative drug industry in the world. I have overwhelming respect for the ability and ethics of many people at FDA and in the pharmaceutical industry. If my son were sick and needed care, there are plenty of people at FDA and in industry who I would feel comfortable with taking care of him.

What are your perspectives on the Ketek approval?

During the review there were scientific and process issues. The scientific issues were complicated but not insolvable. With respect to safety, there were liver issues, drug interaction issues, cardiac issues, and issues involving vision. The efficacy issue was whether the drug really had been shown to work for less-serious respiratory tract infections, which frequently resolve on their own without antibiotic treatment.

There was also the question of whether the drug was really effective with bacteria resistant to other antibiotics. The company kept saying it was, but their studies were not designed to show that. There was no convincing data that Ketek was more likely to cure patients who had pneumonia due to resistant bacteria. There was no convincing data showing an advantage for Ketek with the lesser infections they wanted approved, which were sinus infections and bronchitis. Antibiotics are not commercially viable if you are just trying to market them for pneumonia. There are just not enough cases in this country. But, given the safety issues, is it medically justified to prescribe Ketek for a sinus infection? A lot of toxic antibiotics are available because they do something useful. For example, penicillin can cause shock due to allergic reactions, but it can also save lives in a variety of infections like meningitis or pneumococcal pneumonia. It all boils down to the risk/benefit tradeoffs.

Part of the problem is that the Food, Drug, and Cosmetic Act sets an unrealistic standard for drug approval. The legal standard for approval is that a product has to be both "safe" and "effective." There is no trade-off in the law between "safe" and "effective." However, the trade-off exists in practice. If you look at cancer drugs, they clearly are not safe in the sense that they almost always cause horrible side effects. But the benefit of the drugs outweighs the toxicities. There is no such thing as a drug that is safe in the sense that nothing can ever happen. When we say a drug is safe, what we are really saying is that the chance of something happening is either very low or the potential consequences are so mild that the risks are outweighed by the potential benefits.

Everybody would be better off – FDA, industry, physicians and consumers – if we said up-front that drugs are dangerous, but the degree of danger varies and the risk we are willing to accept varies with the situation. The leading cause of acute liver failure in this country is

Tylenol. The risk is close to zero, but it's not zero; it depends on the situation. We think of Tylenol as safe, but it's not 100% safe; no drug is. Tylenol is a lot less safe if taken by someone who just drank a lot of alcohol.

At the other extreme, isoniazid is far more toxic to the liver than Ketek, but is absolutely necessary to treat people with TB. FDA should articulate how it will evaluate risk vs. benefit so industry doesn't waste years developing drugs that FDA rejects on an *ad hoc* basis.

What about the Ketek approval process?

The process issues were much more problematic than the science issues. The primary issue was whether or not important data supporting the application was fraudulent. FDA has never addressed this issue.¹ In particular, serious questions were raised about a large study that Aventis (now sanofi-aventis) did to compare rates of serious adverse events like liver problems, vision problems and heart problems, in comparison to another antibiotic, Augmentin.

In a previous study, a subject in Finland had developed serious liver problems after taking Ketek. He became so ill that he had to undergo a liver biopsy, which is unheard of in an antibiotic study. The picture from the biopsy looked very similar to an antibiotic called trovafloxacin that had been marketed in the 1990s and was tied to dozens of deaths due to liver failure. FDA was very concerned because Aventis was preparing for broad marketing of this drug; potentially, millions of people would take it. We didn't want to see a repetition of trovafloxacin. We needed to know if the subject in Finland was a one-in-a-million event and Aventis was just unlucky, or was this something that could happen again and again?

The company did a large study, called "TREAT," with 24,000 patients. The idea, very oversimplified, was that if we didn't see another serious liver event and we didn't see other serious problems, the drug was going to get approved. The data were submitted to FDA in July of 2002.

When FDA reviews an application, we go out in the field and inspect selected clinical sites. We visited the largest enroller, Anne Kirkman-Campbell down in Gadsden, Alabama. The FDA investigator found such serious problems that the case was referred to the Office of Criminal Investigation. When this happens with the largest enroller, you have to ask, "Is this an isolated problem or is there other funny stuff going on here?"

When we met face-to-face with Aventis, they said, "Well, yes, we were aware of some problems with Kirkman-Campbell, but we promise you that there were no problems at any of the other sites." That turned out to be not true. The second-largest enroller had significant problems. The third-largest enroller was a physician on medical probation during the study. Not long after the study ended, he was arrested on cocaine and weapons charges and had his license suspended on an emergency basis by the state of California. We inspected 10 high-enrolling sites; all of them had serious problems. These sites were the most likely to receive intensive monitoring, so what did that say about the other 1,800-odd sites? Aventis has frequently said that there were problems at only a handful of sites. What they don't mention is that only a handful of sites were inspected. Every site that was inspected had significant problems. Four cases were referred to the Office of Criminal Investigations.

We found out later that PPD, the CRO, had warned Aventis that there were serious questions about whether Kirkman-Campbell was really enrolling subjects or just making them up. She was enrolling subjects every few minutes. She was enrolling subjects when her clinic was supposed to be closed. It smelled very much like fraud. There are experienced people at Aventis. There was no way they couldn't have recognized the seriousness of the problems. If they ignored Kirkman-Campbell, what else did they ignore? Kirkman-Campbell

went to jail; Aventis got its drug approved. In my opinion, Aventis knowingly threw garbage data at the FDA and FDA let them get away with it. Why did FDA not investigate whether Aventis systematically covered up the problems?

Just because there is smoke, there is not necessarily fire, but you damn well better look. FDA apparently decided that if it's some small company that can't defend itself, then go ahead and make an example out of them, but not if it's the third-largest pharmaceutical company in the world. You don't want to get sanofi-aventis mad at you. FDA sent a terrible message that good conduct and bad conduct are going to be regarded as the same by FDA, at least if you have political clout.

Was the data from the TREAT study used in the approval process?

The data were presented to a federal advisory committee on January 8, 2003 at a time when FDA knew there strong indications that there were problems at multiple sites. I had sent an email message to the FDA manager who was going to make the decision about whether to approve the drug or not. I specifically told him in writing there were problems with the TREAT data and they might be widespread. He wrote back to me that it wouldn't be "productive" to tell the advisory committee about the problems. What does that mean, it wouldn't be productive? How else are we going to give the committee accurate and reliable recommendations?

I was Safety Team Leader on the drug. I had a reputation of being very easy to work with, somebody who did not raise safety issues lightly. I had been responsible for approving a number of high-profile drugs that had toxicities, but I felt that they were important drugs. If they were going to listen to anybody, it would have been me.

FDA has said, "No, we didn't use the TREAT data." They may have said they didn't, but the evidence indicates otherwise. First, when the initial reports of Ketek-related liver failure surfaced in January, 2006, FDA put up a public health advisory and Q&As about Ketek. One of the questions was what did FDA know about the safety of Ketek before it was approved? They said we examined the results of the TREAT study. My question is, if we didn't use it, why did they cite the study?

Second, the Deputy Director of the Office of New Drugs sent me an email message on March 21, 2006. The message said that, after talking to the review division, she concluded that they had not completely disregarded the results of the TREAT study.

FDA required Aventis to do a postmarketing pediatric efficacy study, without having good data on efficacy or safety in adults.

Despite the process problems, was the decision to approve Ketek medically correct?

Pneumonia is a life-threatening disease, so I could see approving it for that. Bronchitis and sinusitis don't kill people, so, without reliable safety data, I can't see approving it for minor illnesses. As it has turned out, a number of people have died. The index case was a twenty-six-year-old man who took Ketek for an upper respiratory tract infection. He died a horrible death from acute liver failure, bleeding out of every orifice. He left behind two kids. How do you think his physician felt? He prescribed the drug based on FDA's approval.

Other antibiotics all have side effects, but they were not approved on the basis of fraudulent data. We don't know if the data for Ketek is true or not, so patients and their physicians can't assess the risks. However, it appears that reporting rates for liver events have been significantly higher for Ketek than for comparable antibiotics.

What are the prospects for the war on bacteria?

We need to make some paradigm shifts. There are a lot of different ways to fight bacteria. One traditional way, of course, has been antibiotics. The common wisdom is that antibiotics are more expensive to develop than other drugs because you have to do studies for each infection. In fact, if you look at the data, the return on investment for antibiotics is very competitive compared to a lot of other therapeutic classes. Unlike in other therapeutic areas, in vitro lab tests can give you pretty accurate insight into whether or not an antibiotic is going to work in vivo.

We can do more with public health measures. The bacteria responsible for Legionnaires' disease live in cooling towers in hospitals. Legionnaires' is hard to diagnose and hard to treat. It is much simpler to just disinfect the water. If we engage in good infection control practices, patients don't get the diseases. Vaccination works well, but people need to take the vaccine. Don't get me started on using antibiotics to treat minor viral infections.

We need more research into various mechanisms of augmenting the immune system, rather than trying to kill the bacteria. There are also innovative ideas such as using viruses that kill bacteria but don't affect people.

Why does FDA publish a draft guidance and then it just sits there for years?

Let me tell you a story. In August 2004, I was asked to chair a working group to write a guidance for developing products targeting Anthrax. High-priority anti-terrorism stuff. We wrote the guidance in about a year, which may seem like a long time, but it was very complicated scientifically, and legally, and people from all over the FDA had to work on it. It has been sitting in limbo now for two years. Recently, I was contacted by an FDA medical officer who had been put in charge of the project. She asked if I had a copy of the most recent version. I had left the agency a few months earlier.

To get back to your question, there is certainly a lack of resources. But there is overwhelmingly poor management in the Office of New Drugs and the Center for Drugs. Some of these people have their strengths, but some of them could not organize a two-car funeral.

The only thing that really counts now at the agency is getting drug reviews done on time. Other projects, absolutely essential projects, don't matter. Also, there is absolute denial at the upper levels of FDA that anything is wrong. They really, truly don't believe they are doing anything wrong, and they sure don't want to hear it from anyone else.

The new commissioner, von Eschenbach, has the same mindset. This is a man who came to the National Cancer Institute in 2002 and announced that he was going to end pain and suffering due to cancer by 2015. He sends out what are called Commissioner's Comments every Friday to the FDA staff. Back in March, he was accused of lying to a Congressional Committee. The chair of the committee, Representative Stupak, basically said to him, "I don't know if you are trying to mislead this committee or if the people who briefed you are, but we are top of this. Do not do that." A couple days later, von Eschenbach wrote in his Commissioner's Comments about how happy he was to have had an opportunity to brief Congress on the FDA's work. It's all happy-talk.

I have been very critical of FDA, but I think that a lot of the solution is not fault-finding, but saying, "We have a problem; how are going to fix it?" There are some awful managers, but also a lot of good people both at FDA and in the industry.

With all of these challenges, do you see reasons to be optimistic about the future?

Yes. First, it looks like the new drug safety legislation is going to call for more transparency, which will be a huge help to industry. Industry is desperate to know what FDA really thinks. Having clinical trial registries where everyone can see the results, and putting FDA reviews on the web more quickly will help.

Second, it looks like the new legislation is going to tell FDA how to do postmarketing safety analysis. FDA has created different offices, moved them around, and renamed them, but it looks like it will take an act of Congress to get the work done.

While drug companies don't especially want more requirements, they do want some clarity on this question of risk vs. benefit. The third-party payors want it. Patients are going to demand it. Maybe FDA will issue a guidance explaining how it balances risk and benefit.

Note

1. On October 23, 2007, over five years after receiving the TREAT study data, FDA issued a warning letter to sanofi-aventis. The letter is available at http://www.fda.gov/foi/warning_letters/s6551c.htm. Public comments by Dr. Ross, Ann Marie Cisneros, and other critics of FDA's actions related to Ketek may have helped persuade FDA to issue the letter. See: "Red Flags in the Study Office: Ann Marie Cisneros on the Ketek TREAT Study", Norman M. Goldfarb, *Journal of Clinical Research Best Practices*, August 2007, http://firstclinical.com/journal/2007/0708_Cisneros.pdf

Interviewer

Norman M. Goldfarb is Managing Director of First Clinical Research LLC, a provider of clinical research best practices information, consulting and training services. Contact him at 1.650.465.0119 or ngoldfarb@firstclinical.com.