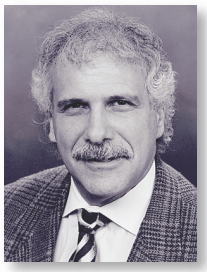
Reflections on Changes at FDA

Eric B. Sheinin

In this article, Dr. Sheinin discusses his personal views on the changes that have occurred at FDA during his 30-year tenure with the agency.



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The relationship between the pharmaceutical industry and FDA has always developed in an environment that was governed not only by the passing of specific laws, but also by changes in attitude that, although less tangible, are just as influential. In my experience during the past 25 years, the FDA milestones that had the greatest impact in the industry were the prescription drug user fee act (PDUFA, 1992), the formation of the Office of Pharmaceutical Science (OPS, 1995), and the FDA Modernization Act (FDAMA, 1997), which came about as a result of Congress passing certain laws. Just as significant, however, was the change in attitude at FDA's Center for Drug Evaluation and Research (CDER).

A friendlier FDA

I spent nearly 15 of my 30 years at FDA in the laboratory working for the Bureau of Drugs, which later became the Center for Drugs and Biologics. When our lab was closed in 1985, I moved into the review area, where the attitude between the industry and the agency was very adversarial. It wasn't more so one side than the other; it was just an adversarial relationship. CDER more or less had an attitude of "We're going to tell you what to do, and you better do it if you want to get your drug approved." The industry accepted that stance and more or less took the "yes, sir" attitude. It was almost as if we had said "Jump!" and the industry would ask "How high?" That relationship wasn't good for anybody. It wasn't good for the agency; it wasn't good for the industry; and it certainly wasn't good for the American public. FDA is now a friendlier FDA, and there's much more cooperation to try to resolve issues to ensure that safe and effective drugs are getting to the American public as expeditiously as possible.

A lot of this change in attitude came about from a change in personnel — people coming in who had a different view and a different outlook. There had been a lot of people at the agency who point blank did not trust the industry. That mistrust existed partly as a result of the generic drug scandal, but it was also there well before that. The attitude was there when I first started in the review area, which was before the scandal, but certainly the scandal made everything worse. Over the years, however, the people coming into the agency had a more liberal attitude and tried to develop an area of mutual trust. If a company did something that destroyed that trust, then that was a different situation — there might be a legal action, or they might be asked to explain what was going on. But my feeling has always been that you trust people until they prove you can't trust them. That's the way the attitude at CDER became, and we had

to begin to trust the industry. I've said at many meetings that the agency and the industry have the same goal of getting safe and effective drugs on the market.

PDUFA

PDUFA seemed to memorialize that goal, or at least it stated very explicitly that everybody was working toward the same goal. First, PDUFA made CDER pay much more attention to project management. The agency did hire a lot more staff, but somebody had to manage the operation. And it became a much more efficient operation by the gradual introduction of the goals and by increasing the targets each year, especially the first five years. By the fifth year, our target was to meet 90% of the goal dates. That forced us to become a much more efficient operation. Just adding people by itself would not have done it. In fact, adding people creates its own problem in managing them. PDUFA made CDER take a look at the way it was operating and how it could operate more efficiently while still giving the same level of review to the submissions so that safety, effectiveness, and quality would not be compromised.

PDUFA also modernized the agency. Because of the PDUFA money, CDER's IT staff was increased, and its computer hardware was updated to the point that every computer was scheduled to be replaced every three years. This ensured that the agency would have up-to-date IT equipment so that it could keep pace with what the industry was doing. That has now led to the point where CDER is nearly ready to go completely electronic. CDER director Janet Woodcock has a goal that by 2002 CDER will be in a position to accept everything electronically. It will not be required by then, but CDER will have the capability of accepting any submission electronically.

PDUFA made a big difference in the industry, and it also changed the relationship between the center and the industry. Some people feel it has given the industry too much power — that PhRMA is dictating how CDER is going to operate. In a sense it did, because through PDUFA it's said what PDUFA dollars can be used for and what they cannot be used for. PhRMA doesn't tell the agency what to do, but they do have a say in how that money can be spent as PDUFA is renegotiated every five years.

OPS

The next big change was the formation of OPS and the creation of the Office of New Drug Chemistry. From my perspective on the chemistry side, I think it went a long way toward creating a much more consistent approach to the review of applications, whether they were INDs, NDAs, or supplements. Before that, chemists were part of the review divisions. When companies that had products that crossed division lines would make certain changes to the CMC portion, they would submit supplements to a number of different divisions. We would hear time and time again that Division X said it's okay and had approved it; Division Y said it's approvable but they need more information; and Division Z said it's not approvable, and it needs more work. They were very concerned about the lack of a consistent approach. This was one of the driving forces behind moving the chemists out of the review divisions and creating the Office of New Drug Chemistry.

In that same timeframe, a lot of work was done on the development of guidances. OPS director Roger Williams was very much responsible for the push to develop guidances that would give the industry information about what the agency was looking for in various areas. That had a very significant effect on how the chemists were doing their jobs. I'm sure there are still some inconsistencies — there always will be when you have more than a hundred people looking at all of the different submissions — but the amount of inconsistency is way down. My feeling even back then was that there wasn't that much inconsistency, but as I look back now things did get better. You must have a balance when developing a consistent approach, which means guidances should be applied by the reviewers as well. There must be a balance between fitting things into a slot and allowing people to use their scientific training to evaluate things. Sometimes that's difficult. Some people have the feeling that everything is being pigeon-holed, but every application is different. Every application presents different issues and different problems that allow people to be creative and use their training and expertise to figure out what's going on while at the same time trying to keep a consistent approach about how to handle impurities, how to handle stability data, how to handle packaging, etc. I think it's a much better way of doing things than we had before. There's direct supervision now over what's going on, and the people in charge of CMC now have supervisory authority over the chemists and the microbiologists.

FDAMA

FDAMA, specifically section 116 that deals with postapproval changes, was also a turning point. That section caused CDER and the areas of the agency concerned with biologics and veterinary medicine to rethink how they were handling postapproval changes. Part of what helped in that regard was SUPAC. SUPAC also represented a significant change in that it provided for a reduction in the regulatory burden over what was in the regulations. It allowed that reduction to occur via guidances, which is a very important part of what was in 314.70(a). SUPAC finally listed in a guidance what kind of information the agency would accept for certain types of changes and what the recommended filing mechanism was.

Now the next step is to establish what criteria could be used to reduce the burden even further. This will be another significant change. **PT**