



Tough Challenges at the FDA

By John E. Calfee

Running the Food and Drug Administration (FDA) is one of the most challenging jobs in Washington. The task of the commissioner is far more complex than simply approving new drugs. Critics of the agency in recent years have been more concerned about possible problems with drugs on the market than about unnecessary impediments to bringing new drugs to market. Too much safety can be as harmful as too little.

President Barack Obama must nominate a new commissioner of the FDA. The previous commissioner, Andrew von Eschenbach, resigned on January 20 when Obama took office. The president has already appointed an acting commissioner, Frank Torti, the FDA's well-regarded deputy commissioner and chief scientist who has been at the agency for less than a year. But finding a permanent commissioner is a different matter entirely. Filling the commissioner post has been agonizingly slow ever since the Health Omnibus Program Extension of 1988 made FDA commissioners subject to Senate confirmation. Individual senators can exercise a temporary veto, and they sometimes pick fights over extremely narrow issues, such as moving a single drug from prescription to over-the-counter status. Having a confirmed commissioner at the helm has become the exception rather than the rule. In the eleven years and eleven months since David Kessler, the first Senate-confirmed commissioner, resigned in February 1997, the FDA has been presided over by acting commissioners more than half the time. The four interim periods without a confirmed commissioner averaged 18.5 months, and none was shorter than fifteen months.

The FDA's immense regulatory ambit is said to encompass one-fourth of the U.S. economy, but

by far its greatest challenges lie in balancing the risks and benefits of both new and approved drugs and medical devices. This balancing act is deeply influenced by outside forces. Watchful critics in Congress, academia, and the practitioner community are quicker to spot something amiss with an FDA-approved product than they are to discern slowness or inefficiency in moving development and approval forward. This one-sided criticism, which in recent years has risen to the level of vitriol, is bound to push the FDA staff toward over-caution and a disproportionate emphasis on safety rather than, say, getting new drugs to market.

It is no surprise that critics have claimed that the FDA, having jumped or been pushed into bed with the pharmaceutical industry, has neglected drug safety. The critics' evidence is, however, primarily anecdotal. For that matter, the two leading controversies—whether the pain relievers Vioxx and Celebrex cause heart attacks and whether certain antidepressants trigger suicidal thoughts in their youthful users—have been largely resolved without any real evidence of FDA neglect. In fact, there is strong evidence that when the FDA responded to critics by imposing stark warnings on antidepressants, the net effect was more suicides rather than fewer because the warnings deterred usage among seriously depressed younger patients. One can criticize the FDA for many things, but the idea that FDA management ever decided to

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slight drug safety in any systematic manner has no foundation in either common sense or the public record.

The next FDA commissioner, acting or permanent, must be a virtuoso balancer and must exercise that skill on a much broader front than most people appreciate. The public tends to focus on the FDA's yea-or-nay decisions on new drugs or new warnings. But that is only a small part of the agency's portfolio. Far more important in the long run are the thousands of decisions made every year about essential details in murky areas such as product development and manufacturing.

Let us hope that the next FDA commissioner remembers that from the standpoint of patients, too much safety can be just as harmful as too little.

In overseeing clinical trials of new drugs, for example, FDA staff have been debating how strongly to rely on so-called surrogate markers—such as blood glucose levels for diabetes, LDL cholesterol levels for heart disease, and tumor size for cancer—instead of “clinical” markers such as limb amputations, heart attacks, and mortality. The agency has also been mulling whether to require that new drugs be not only safe and effective (the traditional standard), but also *superior*—or at least “noninferior”—to the drugs with which they will compete. This seemingly simple topic raises daunting scientific and statistical questions on which leading experts have strongly disagreed. In the meantime, heated discussion has focused on the extent to which clinical trials should be designed to detect rare but serious side effects such as heart attacks or strokes. The FDA recently announced a compromise approach for the most-discussed category—diabetes drugs—without settling the controversy for good.

Meanwhile, there are questions about what kind of testing to require for thousands of annual modifications and improvements in medical devices. Another especially contentious issue is whether to exercise more control over how physicians prescribe drugs and devices, notwithstanding the FDA's longstanding policy of not regulating the practice of medicine. FDA staff and outsiders are also exploring the tricky science of testing “advanced therapies” such as stem cells and autologous therapeutic vaccines. Simply establishing approval standards for manufacturing methods is difficult, not to mention requirements for testing and approval.

The great danger now is that Obama will appoint a permanent commissioner devoted to the politically attractive gambit of pursuing an agenda dominated by a few high-profile issues. Anyone fixated on elevating the prominence of drug safety, for example, is bound to distort decisions even further from reasonable tradeoffs involving drug development and related activities including marketing. The same danger exists for radical changes in FDA approval standards such as downgrading surrogate markers, requiring superiority for new drugs, or forcing dramatically advanced therapies to conform to conventional testing standards. Those changes alone would add years of testing for drugs now in the clinical phase and, worse, would feed back into drug development itself by greatly increasing the expense and length of clinical trials. If the same principles had been applied in the past, immensely valuable drugs would have been greatly delayed or never brought to market at all.

In the ratchet-up world of health and safety regulation, any movement in these directions would be extremely hard to reverse. Yet the FDA is already moving to reduce the role of surrogate markers and to implement a superiority requirement for some drug classes (certain antipsychotics, for example). Let us hope that the next FDA commissioner remembers that from the standpoint of patients, too much safety can be just as harmful as too little.