FDA Faces Multiple Challenges

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Commissioner Crawford's top priority is to restore public confidence in FDA oversight of drug safety and quality.

The controversy surrounding the appointment of Lester Crawford to head the Food and Drug Administration reflects the importance of the post and the difficulty of finding anyone with the scientific and political skills to fill it. Crawford's nomination was put on hold for several months as various legislators sought to pressure FDA to take action on pet issues. Some senators first wanted the agency to decide whether to approve an over-the-counter version of the emergency contraceptive pill, "Plan B," while others pressed for FDA support of broader drug importing.

Senate Finance Committee chair Charles Grassley (R-IA) expressed more general concerns about FDA in criticizing Crawford's failure to tackle drug safety issues along with FDA's "structural, personnel, cultural, and scientific problems."

But by late July, Grassley and most members of the Senate agreed with Republican and Democratic leaders that FDA is better off with a permanent chief than without. And with five years in the acting or deputy commissioner spot, Crawford had obvious qualifications for the job. The new commissioner failed to win unanimous approval from the Senate, however—a sign of a tough road ahead as Congress and consumers continue to closely scrutinize FDA activities and initiatives.

From shellfish to bovine spongiform encephalopathy

The challenge for Crawford is to demonstrate that FDA decisions will be based on scientific and medical evidence—not on pressure from political leaders. He will have ample opportunity to do so. In his first days following confirmation, the new commissioner briefed members of Congress on reports of deaths related to Mifeprex (mifepristone), announced changes in FDA leadership (see "FDA Announces Top Personnel Changes," p. 26), and answered pointed questions from members of the House Appropriations subcommittee that approves FDA's budget.

At the budget hearing, Rep. Rosa DeLauro (D-CT) pressed Crawford to support legislative changes to FDA operations, relating to drug importing and drug safety oversight, as mentioned below. "FDA has not had a good year," she observed, citing flu vaccine shortages resulting from "inept oversight," delayed withdrawals of drugs such as Vioxx, and failure to enforce an animal feed ban to protect against mad cow disease. Other members of the panel raised concerns ranging from low-quality gelatin imports from India to unsafe shellfish, reflecting the broad range of controversial issues facing Crawford.

In his written testimony, Crawford outlined key administrative challenges facing FDA in the coming year. He noted difficulties implementing a new user-fee program for medical devices, which is designed to accelerate the review and oversight of a growing number of increasingly complex medical products. FDA also is responsible for spurring the development of new vaccines and taking measures to protect against bioterrorism, but has few new resources to do so. Crawford acknowledged that the agency could lose 251 employees under the administration's budget proposal for 2006, most from FDA's field force. Such cutbacks necessitate a shift to inspecting the riskiest products instead of trying to increase total site audits overall. And, the agency is beginning a massive move to a new White Oak campus in the Maryland suburbs, a costly and disruptive process (see sidebar, "New approaches at CDER").

Ensuring drug safety

Probably the most important issue on Crawford's agenda is to show that FDA can identify, prevent, and manage drug safety problems. Members of Congress have proposed legislation giving FDA the authority to require manufacturers to change labels to reflect safety concerns and to complete

promised Phase IV studies. Some legislators also want to expand the agency's Office of Drug Safety (ODS) and make it more independent of drug approval activities in the Center for Drug Evaluation and Research (CDER).

FDA officials hope that a panel convened by the Institute of Medicine can provide a road map by July 2006 for revising its system for monitoring adverse events without adding new layers to FDA regulatory operations.

At the July meeting of the Institute of Medicine panel, CDER officials described FDA's current system for capturing and assessing information on drug risks and benefits during clinical trials and after a drug comes to market, emphasizing the importance of continuous interaction between staffers in ODS and the Office of New Drugs. Paul Seligman, who oversees ODS in his role as director of CDER's Office of Pharmacoepidemiology and Statistical Science, also acknowledged that additional resources could help FDA gain more information on drug use and safety issues from health plans and other real-world resources after a drug comes to market.

Crawford was reluctant to openly seek more money or expanded authority to oversee drug safety at the July appropriations hearing. He said that he is "open to discussion" of such proposals, noting that the agency is reviewing industry's record for completing Phase IV studies and may have different views when the review is complete. He also pointed to FDA's Drug Safety Oversight Board and the "Drug Watch" safety information Web site as more appropriate ways to provide the public with drug risk information, a stance that drew sharp criticism from DeLauro and others who felt that bigger changes are needed.

Following the critical path

While addressing charges of inept agency

New approaches at CDER.

In addition to top-level management changes, the relocation of FDA offices for drugs, biologics, and medical devices to the new White Oak campus in suburban Maryland provides reorganization opportunities, as evidenced by important changes in CDER offices and divisions:

- The Office of New Drugs is reassigning several product-review divisions. Some of these changes result from the formation of an Office of Nonprescription Products, which oversees applications for product switches as well as new over-the-counter drugs. A new Office of Oncology Drug Products also has been established, which includes drugs, biologics, and imaging products to treat cancer. Other biotech therapies are being reassigned to relevant new-drug review divisions according to indication.
- The Office of New Drug Chemistry will group all its chemists and other staffers together, instead of having them located with medical reviewers according to disease indication or product type. The new structure aims to provide more flexibility in review assignments, permitting the reassignment of chemists to support divisions according to application volume.

Documenting process understanding.

Along with its staff reorganization, the Office of New Drug Chemistry is launching a pilot program to develop a new approach for assessing drug quality information (see "FDA Pilots New Quality Assessment System," *Pharm. Technol.* **29** [8], 20 [2005]). The program represents the latest effort by the Center for Drug Evaluation and Research to persuade manufacturers to submit more chemistry, manufacturing, and controls (CMC) data in new drug applications to demonstrate that production is under control and that subsequent manufacturing changes can be made without extensive FDA review. Through the pilot, the agency is looking for 12 voluntary CMC data submissions, from different manufacturers and covering a range of product types, to evaluate for this program. The applications should follow the format of the common technical document quality summary and pharmaceutical development section. A special ONDC review team will examine the submissions and determine whether the data demonstrates a manufacturer's understanding of its product and process, including critical quality attributes and sources of variability, to be able to mitigate risks. ONDC Director Moheb Nasr hopes that the pilot will help FDA develop guidance on what kind of CMC data the agency must see to understand where production problems can occur and how the manufacturer can control such difficulties. The unstated promise is that companies able to demonstrate risk management capability could benefit in the future from less agency oversight of manufacturing operations and production changes.

handling of safety issues, Crawford needs to assuage fears among manufacturers and researchers that FDA may require longer and larger clinical studies to avoid bringing high-risk drugs to market. At the July Institute of Medicine committee meeting, Office of New Drugs Director John Jenkins acknowledged the "unintended consequences" of slower drug development and approval: requiring larger trials could prompt sponsors to cancel drug development programs altogether, he said, and longer studies could delay patient access to potentially valuable treatments. But members of Congress on both sides of the aisle don't buy such concerns —especially when they see pharmaceutical companies enjoying apparently huge profits.

Meanwhile, continued focus on drug safety has put FDA's "Critical Path" initiative on the back burner. After issuing its report outlining the critical path to biomedical innovation more than a year ago, FDA still has not published a promised list of critical path opportunities for collaborative research to spur drug innovation. Crawford regularly mentions the importance of pursuing critical path initiatives and now is in the position to show that he can do so.

More changes ahead

Moves to expand FDA oversight author-

ity or restructure agency operations will gain a broader hearing in the coming months as Congress prepares to tackle the reauthorization of the Prescription Drug User Fee Act, which expires in 2007. FDA, manufacturers, and interest groups are gearing up for the debate, which will require Crawford and his staff to articulate agency positions on a host of hot issues:

- **Drug importing.** FDA has opposed permitting individuals and third parties to bring in prescription drugs from other countries, claiming that the agency cannot ensure the safety and quality of such products. This stance has infuriated members of Congress who consider broader importing a good way for American consumers to access lower-cost prescription drugs. Even though it is unclear whether widespread importing would save the public much money, legislators continue to press for legalization of such activity.
- **Generic biologics.** With patents expiring for some $10-billion worth of branded biotech therapies over the next three years, FDA is under pressure to describe a legal and regulatory pathway to provide consumer access to lower-cost biopharmaceuticals. FDA has been examining the scientific and technical issues related to developing and testing follow-on versions of approved biologics, and Crawford said the agency would issue a report this fall describing approaches for developing follow-on protein products. At the House appropriations hearing, Crawford acknowledged that he has changed his thinking in the last three years and now recognizes that improved technology may facilitate the characterization of complex molecules. The challenge for Crawford is to retain incentives for developing new biotech therapies while allowing public access to generic treatments that meet standards for quality and equivalence. Congress is likely to seek legislation that provides FDA with clear legal authority to approve generic versions of biologics that don't fall under Hatch-Waxman rules.
- **Curbs on drug marketing.** Crawford has raised concerns about the increasing volume of direct-to-consumer (DTC) drug advertising, concerns also voiced by leading Republicans and Democrats, as well as healthcare professionals. FDA has been issuing more warning letters for DTC ads, prompting some manufacturers to limit the promotion of newly approved drugs and to avoid airing ads for intimate products in prime viewing time. Pharmaceutical Research and Manufacturers of America (PhRMA) has adopted guidelines to curb objectionable advertising practices, but critics contend that a voluntary approach won't solve the problem. Crawford is expected to give industry a year to see if its guidelines address public complaints; if not, Congress will take up the cause.

Doing more with less

Another challenge for Crawford is to cope

with increasingly limited resources. Bush administration statements on FDA's budget request for fiscal year 2006, which begins Oct. 1, 2005, give the impression that the agency will receive more money and resources to cope with its expanding responsibilities. In fact, FDA faces a real budget squeeze, especially if one leaves out user-fee revenues which are earmarked for specific application-review operations.

In response, FDA is implementing management strategies that focus agency resources on its most vital oversight responsibilities. This approach is most apparent in field inspection operations and agency approaches for ensuring manufacturer compliance with good manufacturing practices (GMPs). Crawford acknowledges that the current "environment of fiscal restraint" encourages FDA to limit field inspections to "highly complex or high-risk drug products and processes." The commissioner will rely on CDER's pharmaceutical inspectorate to help make "informed decisions" regarding which high-risk drug products and processes must be inspected more often, an approach of particular concern to manufacturers.

Similarly, Crawford hopes that FDA's GMP modernization initiative will encourage industry to adopt new technological advances to ensure quality drug production. Systems that demonstrate real-time quality control can allow FDA to reduce monitoring of production lots and plant inspections, and the agency is exploring additional approaches along these lines (see sidebar, "Documenting process understanding").

New management strategies focus agency resources on FDA's most vital oversight responsibilities.

FDA's Office of Regulatory Affairs (ORA) is making changes to incorporate more risk-based approaches in field inspections. ORA Director Margaret Glavin, who succeeded John Taylor in May, recently named three staffers to form a top-level management team. Diane Kolaitis, who has headed ORA's Northeast Region, will oversee field operations. Steve Niedelman, who has worked on bioterrorism and other ORA initiatives, will oversee day-to-day headquarters operations. And David Horowitz, CDER's director of compliance, is on detail at ORA to implement a broader risk-management program, an approach he has been establishing for drugs.

Next year will mark FDA's 100th anniversary, and Crawford is already eyeing opportunities to celebrate the agency's achievements in ensuring public access to safe foods and innovative medical products. This celebration will coincide with FDA's relocation to White Oak, a move that Crawford regards as heralding a new chapter in FDA's history. For the first time in decades, the agency's multiple operations will be housed in close proximity, making it easier for them to interact and collaborate. But for patients and policymakers to share Crawford's enthusiasm, the new commissioner must convince his critics that FDA is up to the task of keeping truly dangerous medical products out of patients' hands while supporting continued biomedical innovation. **PT**