Major Changes Ahead for FDA

Jill Wechsler

FDA is consolidating oversight for drugs and biotech therapies, overhauling GMPs, expanding to counter bioterrorism—plus gaining a new FDA commissioner to oversee all these initiatives.

After months of speculation and delay, in September the White House finally nominated its lead health policy advisor, Mark McClellan, as the next FDA commissioner. McClellan, who is a physician and an economist, currently serves on the White House Council of Economic Advisors as the key Bush administration spokesperson about health issues. As a medical doctor with no direct ties to the pharmaceutical industry, he fits the basic criteria set for confirmation by the Democrat-controlled Senate.

Speculation about McClellan's appointment to head FDA had been circulating around Washington for several months, but he was too involved in negotiations concerning Medicare policy and prescription drug coverage to change hats any earlier. The 25 September announcement generated expectations that the Senate would approve the nomination quickly enough to allow McClellan to move into the FDA post this year.

The Senate confirmation process provided an opportunity for Sen. Edward Kennedy (D-MA), chairman of the Senate Health, Education, Labor, and Pensions Committee, and his colleagues to probe McClellan's opinions about drug safety, agency reorganization efforts, and access to medical products, among many other topics of national concern. The new commissioner differs from his predecessors in that he has little direct experience with FDA regulation and policy and has been more involved with health-payment and cost-effectiveness issues.

In addition to having prime credentials for the job, McClellan also benefits from strong ties to Texas politics and to the White House. His mother is the Texas state comptroller, and his brother, Scott McClellan, is the current White House press spokesman. Mark McClellan earned a medical degree from Harvard and a doctoral degree in economics from MIT. He previously held a post in the Clinton administration and is not considered a political ideologue. In fact, he garners praise on all sides for being open minded and conscientious—important traits for anyone overseeing an agency that regulates a broad range of critical consumer products.

Full plate at FDA

As FDA commissioner, McClellan will be expected to tackle several difficult administrative and policy initiatives as well as manage a growing agency. In the absence of a permanent leader, FDA deputy commissioner Lester Crawford has overseen these tasks and has demonstrated strong leadership skills and a willingness to address thorny issues. McClellan will do well to encourage Crawford to continue as his right-hand advisor, a role that can compensate for the new commissioner's lack of administrative experience.

In August, Crawford launched a major agency reexamination of good manufacturing practices (GMPs) (see the sidebar, "Changes in the design and implementation of GMPs" and *Pharmaceutical Technology*'s October 2002 "Washington Report" column). This action is part of the agency's broader shift to risk-based regulation, an approach that aims to focus FDA's limited resources more sharply on high-risk products and activities. At the same time, a boost in resources and personnel to support antibioterrorism activities has expanded the agency significantly. It has experienced its biggest growth in the past 30 years, Crawford noted at the PDA/FDA Joint Regulatory Conference in September. The agency has gained 800 more employees in the past nine months to create a staff of more than 10,500.

Another important initiative is FDA's reexamination of its legal authority to regulate commercial communication related to drugs and other regulated products. The agency published a request for comments about this topic several months ago

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FDA is focusing its limited resources on high-risk products and activities.

as part of a broad review of its policies regarding prescription drug advertising, product labeling, drug marketing to physicians, and additional communications controversies affecting public health.

Crawford described the past year as "the most important legislative year in FDA's history." The Bioterrorism Preparedness and Response Act turned FDA into a "bulwark against potential attempts to contaminate the products we regulate," he commented. Half of the newly added FDA staff are working in the agency's field force, largely to monitor imports that could threaten the nation's food supply as well as waylay counterfeit medical products at the country's borders. FDA also is expanding its network of laboratories so that it can detect outbreaks of food-borne and other diseases.

Moreover, the public's concern about health issues marshalled support for new initiatives to strengthen FDA oversight of pharmaceuticals under the Prescription Drug User Fee Act (PDUFA), which Congress reauthorized in June. A significant change in the act increased FDA surveillance of new drugs during their first years on the market.

Shift in biologics

Probably the most challenging initiative on FDA's plate is the proposed transfer of oversight for therapeutic biotech drugs from the Center for Biologics Evaluation and Research (CBER) to the Center for Drug Evaluation and Research (CDER), which was announced 6 September 2002 (see *Pharmaceutical Technology*'s September 2002 "Washington Report" column). Under the plan, CBER will retain authority over vaccines, blood and blood products, and a new office overseeing gene therapies, somatic cell products, tissue-based products, and other cutting-edge developments. The regulation of monoclonal antibodies and proteins will move to CDER next year, along with the necessary staff, laboratories, and resources to support regulation of these products.

FDA's increasing responsibility for countering bioterrorism plays a role in this major organizational change, Crawford explained. The move will allow CBER to focus its expertise on vaccines and blood products, which are "critical for our homeland defense," he commented at the PDA conference. In the face of growing criticism of the change, Crawford took pains to highlight CBER's supporting role in the development of new therapies and vaccines to combat emerging disease and protect public health. He noted that CBER will retain responsibility for gene therapy and tissue transplantation, which he described as likely to be "the great vehicles for medical progress in this new century."

Changes in the design and implementation of GMPs

Since announcing its GMP initiative in August, FDA has continued to develop its road map for overhauling manufacturing standards for drugs and biologics. At the PDA conference in September, FDA deputy commissioner Lester Crawford said that the agency plans to extend the initiative to foods, a move that will be facilitated by the publication of long-awaited GMPs for dietary supplements.

One innovation arising from the GMP reevaluation will be the development of a team of field inspectors dedicated to inspecting pharmaceutical manufacturing facilities. This team will be similar to the Team Biologics approach adopted for GMP inspections of vaccines, blood products, and biotech therapies and fits the planned consolidation of biotech drug regulation in CDER.

Another FDA goal is to harmonize GMPs with those of other nations. Crawford noted at the PDA conference that he had met with regulatory authorities of the European Union in August to discuss FDA's GMP revision plan. His aim is to fit US GMPs with those of Europe, Japan, and other nations, a plan that may be addressed by the International Conference on Harmonization (ICH). In the past, ICH participants have shied away from tackling GMP standards, which are considered much more complex and variable than the recently adopted manufacturing standards for active pharmaceutical ingredients. However, chances are good that the topic soon will be added to the ICH agenda.

FDA also may become a member of the Pharmaceutical Inspection Cooperation Scheme (PICS), which offers another venue for US involvement in international efforts to harmonize GMPs and policies for inspecting pharmaceutical plants. Although FDA compliance and regulatory officials have participated in PICS training sessions and other meetings, the door was opened for US regulators to officially join those from Europe and other industrialized nations in this organization when PICS was changed from a formal treaty to a discussion forum.

New GMP policies and risk-based strategies that alter the timing of FDA plant inspections will require the industry to change some of its attitudes, Crawford commented, but "change we must." Responsibility for implementing new inspection strategies now falls to John Taylor, who was recently named senior associate commissioner for regulatory affairs and head of FDA's Office of Regulatory Affairs (ORA). Taylor replaces Dennis Baker, who led ORA since 1999; after a transition period, Baker will return to Texas to be in charge of FDA's regional office in Dallas. Taylor is the first lawyer to head ORA. He previously worked in FDA's Office of the Chief Counsel (OCC) and in the commissioner's office, and he has headed ORA's Office of Enforcement for the past two years. In that position he has been involved in implementing FDA's new policy requiring OCC review of all warning letters before they are sent to manufacturers.

In a memo to FDA staff announcing the change, Crawford explained that he had examined many options for improving review processes of drugs and biologics during the past year and that shifting therapeutics to CDER made more sense than completely combining the two centers. At the PDA conference he emphasized the importance of retaining five centers at FDA. He observed that a move in the 1980s to combine the regulation of drugs and biologics into one center had failed and led to the separation of the two units five years later. He said that five FDA center directors was the "right number" for the agency and that he wanted to

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avoid any move that would undermine the "great strengths of CBER."

These comments reflect continual FDA efforts to devise a workable plan for regulating drugs and biologics. Although CBER and CDER have been separate agencies since 1987, they have made numerous efforts to harmonize filing requirements and regulatory procedures to facilitate manufacturer compliance and new drug development. Several streamlining initiatives were codified in the FDA Modernization Act of 1997, and a main goal of PDUFA has been to establish common standards and time frames for reviewing market applications for drugs and biologics.

A difficult undertaking

Crawford acknowledges that consolidating the review of drugs and biologics under one roof is a "very sensitive undertaking." The high-level transition team headed by FDA senior associate commissioner Murray Lumpkin must first determine which biotech products should be reviewed by CDER. The stated objective of the change is to consolidate FDA review of medical products that are similar in clinical development, clinical data analysis, and use in medical practice. However, it is not clear if authority over therapeutic protein vaccines or recombinant blood products should remain with CBER or be shifted to CDER.

Decisions about which product categories will be apportioned to each agency will affect the individual assignment of CBER reviewers to CDER new drug review offices. They also will determine which CBER compliance and advisory functions and which personnel responsible for quality control matters and postmarketing surveillance will shift to CDER. Although Crawford emphasizes that the consolidation will not give rise to staff reductions, there is considerable uncertainty in the agency about how the change will affect CBER's research-review model. Several observers predict a major brain drain from the agency as top scientists leave for academia, research institutes, and industry.

Although manufacturers publicly support the change, some privately acknowledge that their complaints about CBER's drug development requirements and slow application reviews aimed to improve the center's management and systems and never were intended to instigate such a major organizational change. During PDUFA negotiations earlier this year, industry had argued for policy changes to prod CBER to approve more applications in the first review cycle and reach agreement with sponsors about product development programs.

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The dispute gained the spotlight during the congressional investigation into ImClone's development of the colorectal cancer therapy Erbitux. At a June hearing before the House Energy and Commerce Committee, members of Congress criticized CBER officials for permitting ImClone to file a license application for what appeared to be an inadequate therapy-development program. The investigation by the House panel into the insider trading scandal raised congressional inquiries into significant differences between CBER and CDER regulatory practices.

Shifting regulation of biotech therapies to CDER has raised concerns among scientists and other observers. At a CBER symposium held at the National Institutes of Health in September to commemorate 100 years of federal regulation of biological products, gene therapy researcher French Anderson, now director of the Gene Therapy Laboratories at the University of Southern California, termed the breakup of CBER "shortsighted" and "irresponsible." He acknowledged that it often is difficult to work with the agency but that a good deal of CBER demands for studies and data are important. Jay Siegel, director of CBER's Office of Therapeutics Research and Review (OTRR), maintained that the time it takes his office to approve products compares favorably with the process for approving drugs and that no therapies approved by OTRR have been recalled for safety reasons.

Although it may be logical to merge the medical and clinical review of biotech therapies with the oversight of drugs for similar diseases and conditions, a much trickier task will be to transfer to CDER responsibility for reviewing and evaluating chemistry, manufacturing, and controls data regarding biotech products. Clinical testing of drugs and clinical testing of biotech therapies have become more similar, but production methods for biologics remain very different from those for conventional drugs. Biotech manufacturing involves live substances and is not entirely standardized, notes one FDA quality control expert. Moreover, new production methods continue to emerge. Manufacturers acknowledge their concern about having to meet different standards and follow new procedures at CDER, where reviewers may not have a full understanding of biotech manufacturing science.

Biotech companies' likeliest fear is that the shift to CDER will open the door to generic biologics. Manufacturers welcomed earlier assurances from Crawford that there would be no change in statutes governing biologics, laws that now form a high barrier to generic versions. However, under

the new plan these products will be regulated by CDER officials who are very familiar with generic drug policies and have indicated interest in exploring options for the development of therapeutically similar biotech therapies.

FDA officials expect to have a plan for implementing the new regulatory structure for drugs and biologics before the end of the year as numerous working groups iron out the details. Deciding what programs and personnel will go where is not an easy process. CBER and CDER's differing standards for electronic submissions are a problem, as are their differing field inspection programs. CBER funding will be a critical topic because the agency stands to lose about three-quarters of its user-fee revenues. Biotech companies planning to file new license applications in the next few months fear a slowdown in the approval process. The long-term expectation is that a more streamlined regulatory and review process could spur biotech R&D, but change is always disruptive and will present new challenges to regulators and to industry. **PT**

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Global Health Forum

The Biotechnology Industry Organization (BIO) and the Bill and Melinda Gates Foundation are sponsoring the Partnering for Global Health Forum, to be held 3–5 December 2002 in Washington, DC.

The purpose of the event is to bring together leaders from biotechnology and pharmaceutical companies, various government-agency procurement officials, public and private investors, key international health experts, and leaders in academic institutions and nongovernmental organizations to exchange information and ideas that will benefit global health efforts. Scheduled plenary speakers include Elias Zerhouni, MD, director of the National Institutes of Health (Bethesda, MD) and Laurie Garrett, a science and health writer and recipient of the Pulitzer, Polk, and Peabody Prizes.

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