Electronic Information Systems

New Systems Promote Drug Development and Patient Safety

Jill Wechsler

FDA expands electronic data submission programs to improve regulatory operations and ensure appropriate and safe drug use.

Federal health officials are taking steps to establish national electronic medical records and health information systems. The aim is to improve patient care by making it easier for healthcare professionals to access information about medical products and patient health issues. The ability to prescribe drugs electronically is a key element that is critical for reducing medication errors and improving patient compliance.

FDA has launched an ambitious program to support these efforts, beginning with a new rule that will require drug manufacturers to file product labeling information electronically. The agency is developing systems for the electronic submission of applications for testing and marketing new drugs and for capturing information about new drug use in the real world. These initiatives will help build databases containing product safety, efficacy, and quality information about medication use through the National Library of Medicine. The public will have access to this information.

These programs build on a series of FDA policies issued in recent years to clarify how the industry can submit required regulatory documents in electronic format. In January 1999 FDA published a guidance about formatting electronic submissions, which was updated in a new draft guidance published October 2003. A November 1999 guidance addresses the submission of abbreviated new drug applications (ANDAs) in electronic format. In August 2003 the agency issued recommendations for the electronic filing of the common technical document. This standard establishes a new format for registering new drugs around the world based on recommendations from the International Conference on Harmonization (ICH). ICH agreements also are changing FDA policies for the electronic submission of postmarketing expedited safety reports and periodic adverse drug events reports. In addition, FDA is working to clarify its electronic records and signatures policy within 21 *CFR* Part 11 to help manufacturers develop electronic recordkeeping and filing systems.

E-labeling first

Until now, FDA e-submission programs have been voluntary for pharmaceutical companies. The agency has been encouraging e-filing by formulating uniform standards and terminologies for submitting electronic data. The goal is to help manufacturers develop information systems that can interrelate to capture complex information about medical products, practices, and health conditions and transfer the data through secure networks.

Progress in laying a foundation for electronic data submission and evaluation is prompting FDA officials to move forward with mandated electronic data submissions, starting with drug labeling information. FDA issued a final rule in December 2003 that requires drug manufacturers to submit in electronic format the content of package inserts or professional labeling, including all text, tables, and figures (1). The rule establishes a standard format for filing market applications and supplements for new drugs and biologics, including generic drugs.

The aim of the e-labeling policy is to improve the review process and speed up dissemination of labeling changes and important product information to doctors and patients. The data will become part of an electronic library of labeling information for all FDA-regulated products. The system will make it easier for people to search for information about drug side effects, comparisons with other drugs, and product benefits. FDA is collaborating with the National Library of Medicine's DailyMed project, which provides medication information to the public.

In announcing the e-labeling requirement at the 9 December 2003 meeting of the National Council on Patient Information & Education, FDA Commissioner Mark McClellan observed that "using modern information technology to improve public health is no longer optional at FDA." He expects the new program will allow manufacturers to quickly provide FDA with updated information about drug risks and benefits. The information will then help physicians and

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Promoting pediatric testing

In addition to adopting the landmark Medicare reform legislation, before leaving Washington in December 2003, Congress approved several measures of interest to pharmaceutical companies.

The legislators finalized a bill that codifies FDA's pediatric rule, thereby providing the agency with the authority to require drug manufacturers to test the safety of new drugs in children. Industry initially opposed the 1998 rule as unnecessary and beyond FDA's authority. After a lengthy legal battle, a federal court struck down the policy in 2002, and FDA officials decided to seek explicit congressional authority for the policy. With the voluntary pediatric testing incentive program now well established, manufacturers decided not to object. The legislation authorizing the pediatric rule expires in 2007, as does the incentive program, providing a timeframe for Congress and industry to reevaluate the effectiveness or burden of both policies.

Another bill gives FDA some additional revenues by authorizing user fees to support the review process for new veterinary drugs. The Animal Drug User Fee Act was signed into law in November 2003 and will provide approximately $4 million in fees this year to support activities of FDA's Center for Veterinary Medicine. Fee revenues may rise to $10 million per year by 2006.

consumers make "head-to-head comparisons between drugs so that they can make the best choices," he noted. The new initiative is "the first step in developing an electronic library of all FDA labels that can be readily searched and used by professional and consumers alike" and reduce the need for doctors to search through thousands of pages in reference books.

As far as new mandates go, this one is not highly controversial. Most large pharmaceutical companies have been submitting labeling information electronically for some time on a voluntary basis, and the technical process for doing so uses portable document format (PDF), which is inexpensive and widely available. FDA reserves the right to recommend new file formats and software in the future as technology advances but promises to consult with the industry and provide ample warning before making any changes.

FDA published a proposed e-labeling rule in May 2002. The agency received only a few comments and finalized the proposal with little change. The e-labeling requirement becomes effective in June 2004 and applies only to the content of the package insert, including references in annual reports, and not to all the various types of labels on packages and containers or submitted with advertising material.

FDA officials anticipate this policy will greatly facilitate its review of thousands of labeling changes submitted each year. When a manufacturer files even a minor change in professional labeling, the agency must conduct a manual word-for-word comparison using two paper copies.

Further regulations for restructuring the content of professional drug labeling to make it more readable and useful to prescribers are still to come. A related initiative intends to replace paper package in-

serts with electronic information. Pharmaceutical manufacturers support this campaign and have been working to reduce opposition from pharmacists. Tests of a paperless labeling system are underway.

Ambitious plans

The e-labeling rule is just one part of a broader FDA strategy for spurring development of a national electronic health information system. At a speech before the Urban Institute in Washington, DC, in November 2003, McClellan described his vision for using modern information technologies to collect and analyze adverse event information and thus deliver "safer, higher value, and less costly medical care" (www.fda.gov/oc/speeches/2003/urbaninstitute112.html). These initiatives include the following.

Electronic data systems for clinical trials. FDA is collaborating with the National Cancer Institute (NCI) to establish the Cancer Biomedical Informatics Grid, which includes an electronic system for the submission and evaluation of information from cancer trials. A first step announced in November 2003 is to implement a system for submitting investigational new drug applications (INDs) for cancer therapies electronically to FDA. The goal is to build a system that will link cancer researchers in the United States to FDA to allow the electronic submission of clinical data. The process will enable FDA to review these applications faster, thereby expediting new treatments to patients at a lower cost.

The larger goal for FDA is to use this experience with NCI and cancer therapies "as a model for how we manage information across all of the different therapeutic areas and in every clinical trial," McClellan said. Working in the cancer area will further this effort because many cancer researchers and NCI cancer cooperative groups currently use advanced information systems. Investigators in these groups already are entering clinical information electronically, providing evidence of how this process can speed up the clinical trial process and provide information more readily to drug developers and FDA reviewers.

In addition to enhancing FDA's review process, electronic data from clinical trials will accelerate clinical research by allowing researchers to quickly obtain answers to questions about test treatments. Research information data banks can provide useful information about the benefits and risks of drugs to patient subgroups, including racial and ethnic minorities, women, children, and seniors.

Analysis of pharmacogenomic information. FDA issued a proposal in November 2003 to encourage drug researchers to share information with FDA about how genetic differences cause patients to respond differently to therapies (2). Drug manufacturers are collecting more pharmacogenomic data but are reluctant to submit them to FDA for fear that the data might raise red flags for the regulators. The draft guidance clarifies when such data should be filed as part of an new drug application or biological li-

Trade negotiations address pharma pricing

In response to the continuing debate concerning drug reimporting, federal officials are promoting efforts to narrow the differences between pharmaceutical prices in the United States and those in other industrial nations. This approach recently moved into the international trade arena. In talks with Australia about a free-trade agreement, US trade officials sought modifications in Australia's policy for imposing low prices on prescription drugs. US Trade Representative Robert Zoellick included a provision for loosening price controls on drugs in a list of issues discussed during the final round of talks in December 2003. Although Australian officials insist that they will not reduce access to affordable medicines for its citizens, they are eager to boost exports to the United States. Drug prices in the relatively small Australian market are not a prime concern of marketers, but any agreement by that country to soften price controls could set a model for similar trade deals with other nations.

The idea that pharmaceutical prices might drop in the United States if other wealthy nations let their prices rise is a prime theme for FDA Commissioner Mark McClellan. At a Global Medicine Forum in Washington, DC, in December 2003, McClellan observed that drug prices are higher in the United States because the government does not regulate them directly. He added that the current system is not sustainable because Americans will not pay such a large share of R&D costs in the future. McClellan backed the use of bilateral trade negotiations to encourage other nations to pay higher drug prices.

The Medicare reform bill also addresses the issue as part of a provision about drug reimportation. Although the bill blocks broader reimporting, it calls for further study of drug import issues. HHS will conduct a comprehensive study about whether drug importing can be made more safe through changes in the pharmaceutical distribution system and the use of anticounterfeiting technologies.

The conference report to the legislation calls for US health and trade officials to report about the drug pricing practices of other industrialized countries and whether these practices might be considered nontariff barriers to trade. The study will identify those countries with drug price controls and assess how such pricing policies may boost costs for US consumers.

Congress also instructs trade and health officials to analyze whether bilateral or multilateral trade negotiations provide an opportunity to address pharmaceutical price controls, noting that a 2002 trade bill calls for the government to take action to eliminate price controls among US trading partners. The Medicare bill specifically asks trade officials to report to Congress about how these issues are addressed by the US–Australia Free Trade Agreement under negotiation.

cense application. The agency also defines another pathway for providing research information separate from official submissions to help improve regulatory processes and inform the research community.

The initiative involves using electronic information systems to analyze vast amounts of data that can then be made available to the medical community. FDA says it will combine pharmacogenomic information submitted electronically to

camouflage the sponsor while generating useful information about which treatments are likely to be more effective or more safe for certain patients.

Tracking drug products. FDA is finalizing a proposal that was issued last year that requires national product codes on all prescription drugs, biologics, and blood products to prevent dispensing and administering errors. Implementation requires establishing large data banks to collect and distribute product identification information. The regulation is expected to encourage hospitals and clinics to adopt barcode readers and electronic record systems that can read and interpret drug barcode information.

Drug barcoding also may help curb distribution of unapproved and illegal drug products. FDA's Counterfeit Drug Task Force is encouraging several technologies, including an electronic track and trace system that is capable of following a drug from the manufacturer to end users. The purpose is to encourage the use of radiofrequency identification systems and barcodes to establish electronic pedigrees, replacing cumbersome paper-based systems. Manufacturers are testing new tracking technologies and exploring approaches for establishing integrated databases that can be used at all stages of the drug distribution system.

Increased information about adverse drug events. To ensure the safe use of medical products after they are approved for market, FDA is expanding its current spontaneous adverse event reporting system and adopting innovative statistical methods to identify signals of drug problems more quickly. But because this voluntary reporting system is fairly limited, FDA also plans to establish broader active surveillance systems to improve its capacity for detecting drug safety issues. Some initiatives involve linking directly into electronic medical record systems of healthcare plans to scan medical records for signals that could indicate problems with new medical products. Once hospitals

New team at HHS

The task of implementing the complex Medicare modernization legislation will fall to new staff at HHS. One of the worst kept secrets in Washington last year was that Tom Scully, administrator of the Centers for Medicaid and Medicare Services, was packing his bags. In announcing his departure in early December 2003, Scully said he stayed longer than planned to help engineer enactment of the Medicare legislation.

It also is no surprise that HHS Secretary Tommy Thompson is talking publicly about his plans to leave his job after the November elections. Thompson already is focusing his attention on international AIDS programs and preventive healthcare and giving little attention to day-to-day department operations. Thompson will be at HHS when the new Medicare pharmacy discount card rolls out, but not long enough to see all the rules and regulations emerge to implement the pharmacy drug benefit program. Thompson's departure already is generating speculation that FDA Commissioner Mark McClellan could be his replacement—if Bush wins another term in the White House.

and physicians establish electronic medical records systems, adverse event reporting could become an automatic process.

Electronic prescribing systems. The emergence of low-cost Web technologies and an increased use of palm-sized devices among physicians promise to boost e-prescribing to reduce errors and improve treatment decisions. Although e-prescribing is used on less than 10% of drug prescriptions today, McClellan estimates that implementing e-prescribing across the United States could eliminate more than 2 million adverse drug events each year.

FDA's e-labeling policy will encourage e-prescribing, McClellan believes. In addition, an important but less-noticed provision in the recently approved Medicare reform bill supports the development of e-prescribing programs. Although the legislation stops short of mandating health plans and providers to adopt such systems, the measure grants strong incentives to do so. First, it instructs the Department of Health and Human Services (HHS) to establish e-prescribing standards: initial standards will be developed in two years, with input from standards organizations, providers, pharmacists, and pharmacy benefit management companies. HHS will conduct a one-year pilot in 2006 to test the system and issue final standards in 2008.

The bill also provides grants to assist prescribers who are installing e-prescribing programs and, even more innovative, allows Medicare managed care plans and pharmacy plan operators to pay bonuses to doctors and hospitals that participate in e-prescribing programs. One year after the adoption of final standards, all Medicare providers must follow the new standards if they want to use e-prescribing systems. E-prescribing is expected to encourage physicians to comply with drug formularies to improve patient safety and quality of care and yield cost savings.

References

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2. FDA, "Draft Guidance on Pharmacogenomic Data Submissions," www.fda.gov/cder/guidance5900dft.pdf November 2003. **PT**