Washington REPORT

Changes and Challenges for CDER

Jill Wechsler

The proliferation of medical products in recent years, combined with increased pressure to make the drug regulatory process more efficient and effective, is prompting the Center for Drug Evaluation and Research (CDER) at FDA to adopt new approaches to how it oversees the process for developing and approving new drugs. The past 20 years have been the "era of drug effectiveness," says CDER director Janet Woodcock. The coming decades, she predicts, will focus more on drug safety and the need to maximize benefits and minimize risks associated with medical products.

Janet Woodcock, Center for Drug Evaluation and Research (CDER) director, is relating regulatory policies to product risk while seeking to make CDER more efficient and effective.

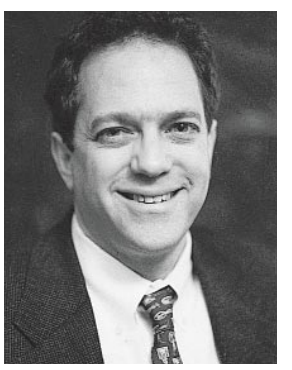
FDA wants manufacturers to help improve risk communication and to be more accountable for what happens to drugs after they are on the market. This shift will not necessarily require new regulations or onerous limitations on all products, Woodcock emphasizes. CDER has developed strong risk-management programs for certain products that pose serious health risks if used improperly such as Thalidomid (thalidomide), Accutane (Isotretinoin), and Mifepristone/RU 486 (Mifeprex). But Woodcock expects that very few products will warrant tight controls because FDA can't manage hundreds of elaborate limited-distribution programs.

One important strategy in terms of quality is to reduce regulatory controls for well-understood and low-risk products. FDA is examining programs that focus plant inspections on more high-risk products and processes and that limit supplements filed on manufacturing changes to more difficult drugs. Woodcock also sees opportunities to ensure drug product quality with less FDA oversight by encouraging companies to apply new technologies to the manufacturing process. Drug companies know how to make quality products, she comments, but they don't always do that. She supports efforts to bring a modern understanding of process controls to manufacturing operations and also wants to ensure that FDA regulations do not impede efforts by companies to change processes and to modernize systems.

Internal changes

CDER's emphasis on risk management is visible in some recent organizational changes within the agency. During the past year, Woodcock lost her two main deputies and several other senior staffers. Roger Williams, former director of CDER's Office of Pharmaceutical Science (OPS), departed to become head of United States Pharmacopeia and was followed shortly after by OPS deputy director Eric Sheinin. Murray Lumpkin, who headed the Office of Review Management (ORM), moved from CDER to a position in the office of FDA's commissioner where he has been overseeing agency policy involving bovine spongiform encephalopathy ("mad cow" disease). Both jobs were filled on an acting basis by top CDER staffers, raising speculation that Woodcock was planning a major reorganization of the center.

Sandy Kweder, acting director of the Office of Review Management.



Steven Galson, CDER deputy director.

Instead, in May Woodcock announced a number of relatively minor shifts in offices and assignments. OPS remains as-is under acting director Helen Winkle, with most changes affecting application review and postapproval monitoring activities. Woodcock plans to move several operations out of ORM to reduce its size and enable it to focus more on conducting consistent and timely reviews of new drug applications (NDAs) and supplements. One change, for example, is to shift the staff that handles advisory committees and consultants from ORM to Woodcock's executive operations staff. ORM, which is headed by acting director Sandra Kweder, will change its name to the Office of New Drugs to reflect more accurately the primary function of CDER's five new drug-review offices.

Emphasis on safety

Woodcock's primary innovation is to create a new Office of Drug Safety that will combine several operations involved with postapproval monitoring and analysis. The unit will report to Steven Galson, the new deputy director of CDER, who came to FDA in April from the Environmental Protection Agency. There he was involved with risk assessment and epidemiology issues, and he will play a lead role in addressing these increasingly important topics at CDER.

The new safety office will include the Office of Postmarketing Drug Risk Assessment (OPDRA), formerly in ORM, plus CDER's MedWatch program. OPDRA director Peter Honig will head the core group that addresses drug safety and risk and may reorganize further this growing operation. Galson also will oversee the Office of Biostatistics, now in ORM, which is involved with the analysis of statistical data related to postapproval safety and risk issues as well as clinical and preclinical testing.

Stronger staff

Galson's appointment further strengthens the Office of the Center Director in CDER. In addition to Galson, a number of right-hand aides report directly to Woodcock. These include

- Jane Axelrad, associate director for policy. In addition to monitoring CDER's implementation of new policies and regulations, Axelrad will manage its

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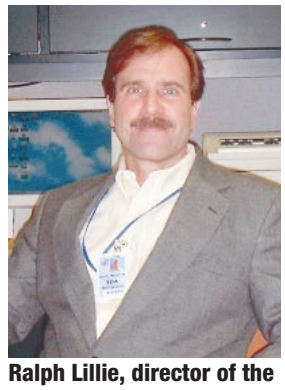
The coming decades will focus more on drug safety and the need to maximize benefits and minimize risks.

freedom-of-information process as part of an effort to streamline and speed up responses to information requests.

- Justina Molson, associate director for international affairs. She oversees CDER involvement with the International Conference on Harmonization and other international issues.
- Robert Temple, director of the Office of Medical Policy and of the Office of Drug Evaluation I in ORM. The Office of Medical Policy includes two divisions that work closely with application review staffs: the Division of Drug Marketing, Advertising, and Communications (DDMAC) and the Division of Scientific Investigations, which inspects clinical research sites to verify data submitted to support NDAs.
- Randy Levin, associate director for electronic submissions. Electronic records have become increasingly important as CDER shifts from paper to electronic submissions of applications, adverse event reports, labeling changes, and manufacturing information.
- Deborah Henderson heads up the executive operations staff, which includes officials in charge of controlled substances, review standards, equal employment opportunity, regulatory policy, and ombudsman activities.

A number of staff offices report to Woodcock. The Office of Training and Communications, headed by Nancy Smith, manages CDER's library, staff training, public affairs, and drug information activities. Russell Abbott, director of the Office of Management, handles the center's budget, operations, and services. The Office of Information Technology, headed by Ralph Lillie, oversees CDER's expanding electronic filing system and data management operations. More familiar to manufacturers is the Office of Compliance (OC), now headed by attorney David Horowitz. OC requests drug manufacturer plant inspections by FDA's field force and sets policy involving manufacturing compliance issues (see "Challenges for compliance" sidebar).



Ralph Lillie, director of the Office of Information Technology.

Randy Levin, associate director for electronic submissions.

New policies from OPS

Although OPS is keeping the same structure, it is examining new ways to become more innovative and efficient. Plagued by limited budget resources, OPS has aimed to do "more with less," says Helen Winkle. However, the newest theme, she notes, is to do "less with less." OPS must review a growing number of applications, many of which are increasingly complex because they involve new technologies. In addition to genomics, the drug development process is presenting novel ways to make new dosage forms. It is a major challenge for OPS to find resources and time to train reviewers.

During the past 30 years, drug development has transitioned from being an art to being a science, observes Ajaz Hussain, OPS acting deputy director and former head of OPS's Office of Testing and Research (OTR). Translating science into regulatory policy is a high priority at OPS, he notes, as seen in the continuing debate about setting appropriate quality specifications.

In addition to these challenges, OPS is

seeking ways to reduce regulatory oversight of low-risk drugs to focus resources on products and projects that require more FDA management. OPS is considering which products are candidates for a risk-based review approach. For the past few months, Yuan-yuan Chiu, director of OPS's Office of New Drug Chemistry, has been discussing the development of a risk-based review policy for chemistry, manufacturing, and controls (CMC) information. The process involves identifying those products that are less prone to product-quality problems and reducing CMC data for most manufacturing supplements. It also would modify the amount of CMC data filed with abbreviated new drug applications for generics. Manufacturers would have to develop scientific and validation data to ensure drug purity, quality, and strength, but this data would be examined during periodic and random inspections performed by a team of CDER review chemists and field inspectors instead of being routinely reviewed by chemists at FDA headquarters.

Yuan-yuan Chiu, director of the Office of New Drug Chemistry.

Helen Winkle, acting director of the Office of Pharmaceutical Science.

Developing a risk-based CMC review policy is one piece of a larger effort to rationalize FDA regulation of the drug manufacturing process. FDA already has reduced the need for manufacturers to obtain agency approval for making certain low-risk manufacturing changes according to its Scale-Up and Postapproval Changes (SUPAC) initiative that was launched almost 10 years ago.

More recently, CDER proposed a Biopharmaceutics Classification System (BCS) to determine which products can rely on in vitro dissolution tests to ensure in vivo bioequivalence. This plan aims to provide another strategy for reducing unnecessary testing to ensure product quality following manufacturing changes. Chiu notes that the new CMC policy looks at all drugs and therapies to identify those that are "rock stable"

Growth for generic drugs

One of the more high-profile operations in OPS is the Office of Generic Drugs (OGD), headed by Gary Buehler. Because generic drug manufacturers decided not to join the prescription-drug user fee program, OGD has suffered from a shortage of budget resources needed to support timely review of a growing number of abbreviated new drug applications (ANDAs). OGD received 365 submissions in 2000 and approved 244 generic drugs, including 52 first-time generic products. The median approval time was 18 months — less than a few years ago but still much longer than the six-month review period called for by Congress.

Buehler has been working hard to make OGD more efficient and received some help from Congress last year. An additional $1.5 million budget appropriation permitted OGD to upgrade its computer system and obtain equipment to enhance staff training and communications. ANDA approvals take 18 months, he explains, because OGD conducts a rigorous review for all applications to ensure that the system is fair in a highly competitive market. Buehler wants to streamline OGD's process for manufacturers to correct deficiencies in applications while also providing more consistency among agency reviewers. OGD also is encouraging manufacturers to file applications electronically and is revising OGD's electronic format to be more consistent with that for NDAs.

To fit CDER's program for reducing oversight of low-risk products, Buehler also is looking for ways to reduce the regulatory burden on "drugs you can't mess up." The agency may curb preapproval inspections for some products based on company history, type of dosage form, and safety experience with the product.

Gary Buehler, acting director of the Office of Generic Drugs.

Buehler believes that OGD could reduce approval times from 18 to 12 months or less with more resources and management improvements. However, many applications are kept off the market by patent disputes, controversies that also impose significant burdens on FDA. Agency efforts to clarify policies for granting a 180-day exclusivity to the first generic product on the market and for 30-month stays in generic drug application approvals when the innovator files patent infringement claims have absorbed considerable CDER resources and generated vehement disputes. Woodcock is planning an education campaign to better inform consumers about the therapeutic equivalency of generics as a way to enhance public acceptance of lower-cost medicines.

Challenges for compliance

CDER's emphasis on relating regulatory policies to product risk is affecting operations at the center's Office of Compliance (OC) headed by David Horowitz. OC works closely with FDA's Office of Regulatory Affairs (ORA) to request field inspections and then reviews the resulting inspection reports to determine what regulatory action may be warranted. Horowitz recently has developed a risk-based inspection initiative that fits CDER's overall policy. This involves providing more guidance to the ORA field force so that it first inspects those firms producing medical products with the greatest public health influence. Horowitz regards compliance as a risk-control activity that aims to allocate resources based on public health risks.

One major initiative involves developing a systems-based inspection model. Joe Famulare, who heads OC's division of manufacturing and product quality, is overseeing implementation of this program, which was pilot tested earlier this year in six ORA districts (New York, New Jersey, Philadelphia, San Juan, Dallas, and Los Angeles) (see *Pharmaceutical Technology*'s "Washington Report" column, March 2001). The program calls for abbreviated inspections of companies and sites with strong histories of good manufacturing practice compliance. The abbreviated inspection is based on a systems approach that covers a plant's quality control system plus one of five additional systems (facilities and equipment, materials, production, packaging and labeling, laboratory controls). Field inspectors can decide which aspects of a plant's manufacturing process are most important for a given profile class or dosage form. The program assumes that if two systems are in compliance, the entire facility is operating correctly; if the two systems have problems, the facility is out of compliance. To make targeted inspections more useful, OC is providing guidance to the field force on risks associated with certain products or facilities, based on data about adverse events and recalls for a certain type of product, as well as whether a manufacturer has had problems with certain aspects of production. Horowitz and Famulare also are working with ORA on a number of significant compliance issues, including

David Horowitz, director of the Office of Compliance.

- Implementation of the Mutual Recognition Agreement between FDA and the European Union (EU) to accept site inspection reports from each other. A number of issues have delayed FDA's ability to determine that the inspection programs carried out by EU Member States are equivalent to FDA procedures. FDA now believes it can determine equivalency by year-end for the United Kingdom and possibly for Ireland and wants to launch the operational phase with just those countries. However, EU officials have adopted an all-or-nothing policy and oppose launching the program for just one or two nations.
- Drug reimportation. Congress is pressing FDA and the Department of Health and Human Services to implement legislation approved last year that would permit pharmacies and distributors to reimport medicines made in the United States but sold at a lower cost overseas. The aim is to make lower-priced pharmaceuticals available to US consumers, but FDA officials maintain they cannot ensure the quality and safety of products that have left the US distribution system. Some members of Congress are upset about the delay in carrying out the policy and are looking for ways to address FDA's concerns about the program.
- Counterfeit imports. The expansion of foreign manufacture of bulk active ingredients has focused attention on the rise in counterfeit bulk ingredients being shipped to US manufacturers. FDA has pressed US firms to check sources more carefully and now says that this problem is diminishing. A larger concern is the expansion of unregulated drugs coming into the United States through illegal channels plus consumer purchases of medicines through Internet Web sites. Patients are finding it increasingly easy to obtain drugs without any prescription, and many of these products have been found to be mislabeled or adulterated. FDA and the US Customs Service recently told a House Commerce subcommittee that they have no means to examine the hundreds of thousands of packages entering the country daily through US ports and post offices. They want to be able to return the imports to the senders instead of having to forward them to recipients, as is now required by law unless they determine that the contents are illegal or unsafe.
- Electronic signatures (ES)/electronic records. FDA has been working with manufacturers to clarify this complex and controversial program. FDA says it is finalizing important guidances in this area, but manufacturers complain that field inspectors already are asking about ES compliance even though requirements are confusing. One major issue is how detailed audit trails have to be and whether they apply to any document.

and require less FDA oversight. Larry Lesko is involved with developing the BCS policy as head of the Office of Clinical Pharmacology and Biopharmaceutics, and Jerry Collins currently serves as acting director of the Office of Generic Drugs (see "Growth for generic drugs" sidebar).

Challenges ahead

The past year has been a time of transition for FDA, Woodcock observes. The presidential elections and the change in administration have put a number of policy initiatives on hold for several months. Even though FDA still lacked a new commissioner as summer came to Washington, agency officials have begun to work with industry and Congress on a number of programs that will require action in the coming months. The Prescription Drug User Fee Act II (PDUFA II) will expire unless it is renewed by 30 September 2002. Legislation to continue this program will provide a vehicle for revisions in the 1997 FDA Modernization Act (FDAMA) and other initiatives (see *Pharmaceutical Technology*'s "Washington Report" column, July 2001).

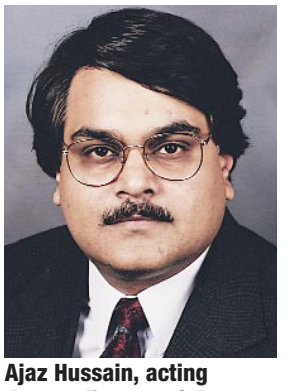
Although no one expects Congress to approve a bill as far-reaching as the measure enacted four years ago, legislators are considering the need for action in several areas that affect drug regulations and FDA operations. One important FDAMA provision expires at the end of this year and therefore must be renewed before Congress takes up PDUFA III and FDAMA. That provision is the pediatric exclusivity program that extends patents for six months for manufacturers who conduct pediatric studies requested by FDA to provide prescribing information for children. In the past three years, manufacturers have conducted some 60 pediatric studies, and FDA has extended exclusivity for almost 30 drugs. Pharma companies are eager to continue this program and are pressing for congressional action before the exclusivity provision sunsets in a few months.

Reducing risk

In addition to preparing for user-fee negotiations and FDAMA revisions, Woodcock is pursuing a number of initiatives to enhance the safe use of prescription drugs by the public. FDA has been criticized by consumer advocates for allowing too many unsafe medicines on the market, just as it faces complaints from manufacturers for demanding more test data than are needed to document product safety and efficacy. Woodcock points out that during the past 20 years, CDER has withdrawn 2.6% of new molecular entities (NMEs) for safety reasons, and that this withdrawal rate is the same today. While recognizing the need to walk a fine line between being overly cautious and approving new drugs too hastily, she notes that the increased number of drugs available and of patients taking multiple therapies creates the possibility of more drug safety problems. These developments are encouraging CDER to do more to collect and assess data about the quality of approved drugs during the postmarketing period.

One important program for evaluating drug safety is CDER's Adverse Event Reporting System (AERS), which combines voluntary ADR reports from its MedWatch program with required reports from manufacturers. Periodic and expedited (15-day) reports filed by industry account for more than 90% of all safety reports submitted to the agency. CDER has expanded AERS in recent years, installing an advanced computerized system that can detect indications of potentially serious, but unrecognized, drug-associated events that can be investigated and tested.

Larry Lesko, director of the Office of Clinical Pharmacology and Biopharmaceutics.



Ajaz Hussain, acting deputy director of the Office of Pharmaceutical Science.

CDER's DDMAC similarly aims to reduce the inappropriate use of marketed medicines by ensuring that drug advertisements and promotional materials are truthful and balanced. DDMAC reviews company materials associated with launch campaigns for new drugs, as well as ongoing direct-to-consumer (DTC) advertising messages. DDMAC is conducting a study of how DTC advertising affects consumers and physicians, who complain that patients are demanding inappropriate therapies because of the influence of high-power television advertising. Critics of drug advertising also insist that industry outlays for expensive ad campaigns are contributing to excessive increases in drug costs.

A major CDER initiative is designed to update and revise FDA policies regarding drug labeling. In fall 2000, the agency published a proposed rule that revises the package insert to make the information more readable and to highlight the most important prescribing information. Manufacturers have complained that the changes would make inserts much longer and require major overhauls of production operations to revise packaging systems. CDER is reviewing these comments and hopes to issue a final rule by the end of this year.

Ensuring product quality

Most FDA proposals to reduce the amount of documentation that manufacturers must submit to support a process change emphasize the need to retain data relevant to these changes for on-site plant inspection. Consequently, FDA conducted more preapproval plant evaluations last year, chalking up 1144 compared with 773 in 1999, although routine good manufacturing practice inspections have been declining (FDA examined 1436 plants in 2000 versus 1844 in 1999). These trends reflect efforts by FDA to reduce redundant inspections as well as make the plant-inspection program more efficient and more focused on high-risk production processes and products (see "Challenges for compliance" sidebar).

In addition to visiting manufacturing plants in the field, CDER takes samples of and analyzes both imported and domestic drug products on the market to ensure conformance with quality specifications. The agency has intensified surveillance of imported drugs because of the rise in import volume. It also selects products for sampling that are NMEs, that have dissolution issues, are highly active drugs, have a history of problems in-

A tall order for CDER

The regulation and surveillance of hundreds of drugs on the marketplace entails numerous programs and processes by CDER. Following is a snapshot of agency accomplishments in 2000 as presented in CDER's *Report to the Nation: Improving Public Health Through Human Drugs:*

- Approved 27 NMEs and 98 new drugs, 20 under priority review. Median total approval time was 11.2 months, and median FDA review time was 10.9 months. Median approval time for NMEs was 15.6 months. CDER also approved three orphan drugs.
- Approved 134 efficacy supplements, with median review and approval times of 10 months.
- Received more than 500 electronic submissions related to NDAs with about 75% of NDAs having some electronically filed components. OGD received 85 electronic submissions for bioequivalence data and 79 for CMC data.
- Approved 1345 new drug manufacturing supplements and 2314 generic drug manufacturing supplements. For new drug supplements, FDA approved 84% in a median of four months. CDER is meeting user-fee goals of reviewing supplements requiring prior approval within four months and changes-being-effected supplements within six months.
- Conducted 1144 preapproval plant inspections, 1085 preapproval inspections for generics, and 1436 good manufacturing practice inspections.
- Issued 4197 export certificates.
- CDER's Web site has grown to 30,000 pages and attracts 600,000 users per month.

volving field alerts or recalls, or are suspected counterfeit products.

OPS's Office of Testing and Research (OTR) conducts scientific studies about drug product quality issues. Recent initiatives have involved developing in vitro methods for studying how excipients and diluting agents affect absorption of orally administered drugs. In a study to better assess the safety and quality of St. John's Wort, OTR identified genetic markers for authentic and contaminated species. OTR works closely with the Product Quality Research Institute on a number of technical issues. The group is developing recommendations for a blend uniformity policy to ensure thorough mixing of a drug substance and product.

FDA regulators increasingly are concerned that quality control efforts may lead to shortages of medically necessary drug products.

FDA regulators increasingly are concerned that quality control efforts may lead to shortages of medically necessary drug products. Shortages have occurred recently because of manufacturing problems, difficulties with bulk suppliers, and company decisions to halt production because of economic or market issues. CDER has developed a Web site to alert the medical community about looming shortages and explain what FDA is doing to resolve them. CDER is trying to work with manufacturers, particularly sole-source producers, to prevent public health emergencies.

For most of these issues, CDER is striving to provide detailed information about policies and programs using FDA's Web site: http://www.fda.gov/ and www.fda.gov/cder/. A wealth of information about CDER activities is available in its *Report to the Nation 2000: Improving Public Health Through Human Drugs,* which is available in PDF format at http://www.fda. gov/cder/reports/rtn2000/. PT