news along the pike

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CENTER FOR DRUG EVALUATION AND RESEARCH

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INSIDE . . .

PIKE'S CORNERS

CDER aims to improve drug manufacturing

Center to build consensus, science base for latest technology

BY PATRICK E. CLARKE

CDER is leading the way to ensure that the pharmaceutical industry can use more efficient and reliable pharmaceutical manufacturing processes. While Americans have the highest quality of drugs in the world, the process used to produce them can be expensive and wasteful.

The Center has observed an increasing trend toward manufacturing-related problems, such as recalls, disruptions of manufacturing operations and the loss of availability of essential drugs, according to Center Director **Janet Woodcock, M.D.** Dr. Woodcock, who worked as a chemist in the industry before going to medical school, noted that manufacturing problems have delayed some new drug approvals.

New technology, which provides continuous in-line and on-line monitoring of industrial processes, could improve pharmaceutical manufacturing and the Center's regulatory processes, according to **Ajaz S. Hussain, Ph.D.**, deputy director of the Office of Pharmaceutical Science. Known as process analytical technology, or PAT for short, it has the potential to provide American consumers with greater assurance of high-quality drugs while reducing costs and time for both industry and the Center.

In most manufacturing facilities, quality control chemists usually only look for the active ingredient or ingredients in a mixture of drugs and inactive ingredients. They remove batches of drug from the manufacturing line, take samples to a lab for testing and document the results for FDA inspectors.

New technology using laser and infrared

(Continued on page 12)

User fee law renewed, review goals retained

The Prescription Drug User Fee Act of 1992 received its third five-year extension as part of the bioterrorism legislation, which became law in June. Details of PDUFA III are at http://www.fda.gov/oc/pdufa/PDUFA3.html. The current law ends Sept. 30.

"Americans deserve timely access to potentially lifesaving new drugs as soon as possible once they are proven safe and effective," HHS Secretary **Tommy G. Thompson** said. "This law will ensure that the FDA has the expert staff and resources to promptly review applications and get safe, effective new drugs into the hands of the people who need them."

The law maintains the high review performance goals of PDUFA II, which included reduced drug review times and increased and accelerated consultations between the FDA and the product sponsors. In addition, PDUFA III remedies resource shortages that affected the program in recent years.

(Continued on page 11)

Center eyes patient information dispensed with Rx medicines

The new Drug Safety and Risk Management Advisory Committee met on July 17 to hear results of an FDA commissioned study of private sector prescription drug information given to patients when they fill their prescriptions and to discuss means to improve the usefulness of that information. About 75 people attended the meeting.

The study, conducted by the National Association of Boards of Pharmacy, showed that 89 percent of patients received written information about the drugs prescribed for them. However, the overall usefulness of the information provided, as measured by eight objective consensus-based criteria, was about 50 percent.

The study was designed to assess the extent and usefulness of private-sector prescription information that patients receive when filling their prescriptions. Study results can be obtained at http://www.fda.gov/cder/reports/prescriptionInfo/default.htm.

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JOE'S NOTEBOOK

History issue; Report to the Nation

As you read the stories in this issue, you should go back in time and imagine a cool spring breeze blowing your hair. I have a lot of catching up to do in this issue and the next. My other projects are done, and I can put the Pike back on track. Please send me your stories and story ideas. The *Pike* will be publishing monthly—or nearly so—once again.

Many thanks to this issue's patient authors who have been waiting for their stories to appear: **Tony Chite, Pat Clarke, Mandy Eisemann, Rich Johnson, Diane Moore, Jim Morrison, Karen Oliver, Tawni Schwemer, Ellen Shapiro** and **Virginia Yoerg.** Unfortunately, I still have a few submissions and stories to get to in the next issue. Hang in there.

Our Center's *Report to the Nation 2001: Improving Public Health Through Human Drugs,* is back from the printer. Regular customers have their copies, and some are in the Medical Library and its branches. If you have already seen it on the Web and would like a durable reference copy or need them for a meeting, e-mail me (OLIVERN). I still have several hundred copies in patriotic red, white and blue.

You can find the Internet versions of the *Report* and PowerPoint slides of its graphs and charts by selecting the About CDER button on our home page (http://www.fda.gov/cder). You can link directly to them at:

- PDF: http://www.fda.gov/cder/reports/rtn/2001/rtn2001.pdf.
- HTML: http://www.fda.gov/cder/reports/rtn/2001/rtn2001.htm.
- Slides: http://www.fda.gov/cder/reports/rtn/2001/rtn2001.ppt.

I'm biased, but I highly recommend the *Report.* It's a useful reference and provides an overview of all our major programs with detailed performance data. The current edition of the *Report* has some changes and additions. The most important of these are how we report our new drug approval statistics, more detailed coverage of counterterrorism and pediatrics and less detailed coverage of PDUFA performance. Here are some highlights of the changes:

New charts for NDA approvals, NME approvals and safety-based NME withdrawals. We're now reporting performance on approvals for standard and priority new drugs separately (http://www.fda.gov/cder/reports/rtn/2001/rtn2001-1.htm#NewDrugReview). The Center feels this method gives a better picture of our performance and its impact on public health than our previous method. Our chart displaying safety-based NME withdrawals is now structured to show pre- and post-PUDFA periods (http://www.fda.gov/cder/reports/rtn/2001/rtn2001-3.htm#Withdrawals).

Counterterrorism. Last year was hardly business as usual, so the *Report* has broad coverage of our immediate response to the last year's terror attacks and our ongoing and long-term work in counterterrorism. It updates information from last year's September-October *Pike* and provides new details as well. You can find the counterterrorism section of the *Report* at: http://www.fda.gov/cder/reports/rtn/2001/rtn2001.htm#Counterterrorism. (Page 5 of this issue of the *Pike* has stories about FDA's Counterterrorism Programs Staff, the finalization of the animal efficacy rule and the move of CDER's renamed Office of Counterterrorism and Pediatric Drug Development.)

Pediatric exclusivity. Our authority to grant pediatric exclusivity has helped us uncover important new dosing and safety information that will help pediatricians and other prescribers use drugs to treat children more confidently. Of the 31 drugs with newly approved pediatric information in their labels at the time of the *Report,* nine had significant changes for dosing, safety or use, and one drug available in several different products was not recommended for pediatric use. You can find these safety details at http://www.fda.gov/cder/reports/rtn/2001/rtn2001-1.htm#PediatricExclusivity.

news along the pike

The Pike is published electronically approximately monthly on the World Wide Web at:

http://www.fda.gov/cder/pike.htm

Photocopies are available in the Medical Library (Parklawn Room 11B-40) and its branches (Corporate Boulevard Room S-121 and Woodmont II Room 3001).

Views and opinions expressed are those of the authors and do not necessarily reflect official FDA or CDER policies. All material in the Pike is in the public domain and may be freely copied or printed.

Have ideas, news or comments to contribute? Please contact a member of the Editorial Board or:

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OMBUDSMAN'S CORNER

If you don't know the rules, who does?

BY JIM MORRISON

Every time I go through the annual agony of doing my taxes, I marvel at the arcane minds of CPAs and of the programmers who devise tax software. I frequently wish there were a software program called *FDA Rules for Dummies.* Let's face it, keeping up with the changes in the laws, regulations, guidances, MAPPs and policies we work with every day is a Herculean task. It is made somewhat easier by the information contained on FDA's Web site and other Internet resources.

Unfortunately, with the increasing exodus of staff with institutional memory, those of us who are left have fewer people we can go to for easy answers. That leads, inevitably, to an increasing number of problems caused by either ignorance of the rules or a lack of experience in interpreting them. That, in turn, leads inevitably to an increased business for the ombudsman.

There are some critical rules that can make a big difference to consumers and to those we regulate if they are ignored or improperly interpreted by CDER staff. Some examples include the rules for:

- Fast track or accelerated approval.
- Pediatric testing and exclusivity.
- Orphan product exclusivity.
- Importation of drugs for personal use.
- Drug manufacturing and quality standards.
- Patent certification for generic drugs.

There are numerous others as well.

No matter what we do or how we do it, there are more people looking over our shoulders than ever before. The news media daily make the public and us aware of our impact on the public health, drug costs and the financial markets. While that has always been the case to some extent, in recent years the public awareness of our activities has increased. The anthrax attacks last fall have also heightened the public's awareness of and expectations for our role in drug regulation.

Whether we are dealing directly with the regulated industry and the public or whether we are scientific reviewers or researchers tucked safely away in labs and offices, none of us can afford to be ignorant of the rules under which CDER operates.

These rules create public expectations that affect our organizational priorities and how we accomplish our mission. Ultimately, they affect how each of us does our work.

Realistically, we cannot individually know every law, regulation, guidance and policy that guides the Center. However, we must have a general knowledge of what rules exist, where they are written and who to ask for advice about their application.

It is also helpful for us to know our larger environment and a little about the forces that impact the Agency. Above all, I urge everyone to be honest about the extent of his or her knowledge. It is no sin to say you don't know. However, winging it can land you in deep trouble.

Fortunately, we have some good resources to help us keep abreast of the rules, policies and environment. The FDA Web site has been improved by replacing its original search engine with Google. Just remember that you sometimes have to search the FDA and CDER sites separately, since you may get some different hits with each.

You can search the Food Drug and Cosmetic Act, other laws enforced by FDA and FDA regulations by going to the Reference Room heading on FDA's Internet home page at http://www.fda.gov/.

The FDA intranet, available to FDA employees only, has a way to keep abreast of the latest news via the Clips, put out daily by the FDA's Office of Public Affairs at http://intranet.fda.gov/clips.

Of course, CDER's Web site has all the guidance documents, MAPPs and policies you need to refer to. The CDER weekly report, circulated by e-mail and posted on the CDERnet lists updates in regulations and other new documents.

Unless we make these resources part of an ongoing learning effort, however, they are of little avail. And, as always, I strongly recommend that if you don't feel fully up to speed on an issue, regulation, guidance or whatever, please ask someone who is.

Jim Morrison is the Center's ombudsman.

Consumer group leaders, Dr. Crawford discuss issues at roundtable

BY ELLEN SHAPIRO

FDA held a consumer roundtable on May 14 in Washington to enable key consumer group leaders to meet with FDA Deputy Director **Lester M. Crawford Jr., DVM, Ph.D.**

The informal meeting for about 15 consumer organizations allowed them to hear those issues that are high on FDA's priority list and to share the concerns of their organizations with FDA's top leader.

The format was informal and began with Dr. Crawford expressing his concerns about bioterrorism, antibiotic resistance, food allergens, chronic wasting disease as well as those relating to risk management and post-marketing surveillance.

Several of the issues brought up by the consumer group leaders included genetically engineered foods and animals, safe medicine use, adverse event reporting, direct-to-consumer advertising and educating consumers about the safe use of dietary supplements.

Many participants said FDA needs to do more to ensure there is an objective source of information available for consumers on the risks and benefits of medicine use.

There was a great deal of interest in the need for consumer guides for medical devices. One consumer group wanted FDA to find new ways to evaluate new foods for allergens. FDA was criticized for spending too much time evaluating public responses to proposed rules and moving too slowly to enforce those rules.

The MedWatch program was discussed, and consumer groups suggested that FDA do more to encourage consumers to report adverse events to MedWatch and to make the program more consumer friendly.

Ellen Shapiro is director of the Division of Public Affairs in OTCOM.

INFORMATION TECHNOLOGY CORNER

IT infrastructure upgrade to speed up network connections

The upgrade to the CDER's IT infrastructure is continuing. Over the past few months, the Parklawn Building, 5630 Fishers Lane, Nicholson Lane and Metro Park North I have been upgraded to new equipment. Upgrades for Corporate Boulevard, Metro Park North II, St. Louis, and MOD I are coming in the future.

You will notice this upgrade immediately when transferring files from the network or Web servers.

The equipment upgrade increases the speed and efficiency of network connectivity and helps you perform your job more quickly and reliably through a more robust network

This upgrade also allows us to better manage the networked equipment and the traffic going over it. Enhanced management features and accurate network traffic statistics will improve planning and help ensure the success of CDER projects.

We are constantly analyzing our IT infrastructure and making enhancements based on priority needs. OIT's Division of Infrastructure Management and Systems will continue to keep you aware of these upgrades and their benefits.

By Rich Johnson (JOHNSONR), an IT specialist with DIMS.

Help Desk FAQ

Is there any way to suppress the font formatting when pasting into Word?

Yes. When you paste text, try the Paste Special option. Using Paste Special will allow you to decide how the information on the Windows clipboard is pasted into your document.

In the case of text, characters copied onto the clipboard can be pasted as unformatted text. This text will look to the style of the destination paragraph. Instead of reformatting the text after you paste it, the text will look just like the rest of your paragraph.

To paste as unformatted text in Word:

- From the menu bar, select Edit and then Paste Special.
- Choose unformatted text in the As: field.
- Click OK.

Paste special also works on graphics.

Contact the Help Desk (CDER Help, 7-0911) for more information.

Resources to track and reduce medication errors increased

BY PATRICK E. CLARKE

The Division of Medication Errors and Technical Support is one of the three divisions in the new Office of Drug Safety (Jan.-Feb. *Pike).*

"The Medication Errors and Information Technology groups were joined to dedicate more resources to look at preventable adverse drug events and medication errors," said **CAPT Jerry Phillips, R.Ph.,** the division's acting director.

The division's mission includes:

- Pre-market review of a product's proprietary name and its associated labels, labeling and packaging for error-prone aspects in effort to reduce the medication error potential of the proposed product. Consultations are received from FDA's other centers.
- Post-marketing review and analysis of all medication errors received in CDER.
- Information technology support to ODS.

"There really hasn't been a change in day-to-day operations for my staff," Phillips said. He does think there will be more dedicated resources to the whole issue of medication errors.

The division is developing computer software to screen proposed proprietary names for sound-alike and look-alike similarities. There are about 15,000 existing marketed proprietary names in the United States. In addition, the division is involved with the review of the container label, labeling and packaging, which can play a critical role in reducing medication errors.

FDA has more than 120 volunteers who participate in prescription writing studies. Phillips' staff does written outpatient, in-patient and verbal orders and lets the volunteers interpret them. "I think it reflects well on the commitment of our people at FDA that we have volunteers from throughout the agency," Phillips said.

He is also pleased with the good working relationship his group has with reviewers in the Office of New Drugs and the Office of Generic Drugs. The medication error staff and a representative of the Division of Drug Marketing, Advertising and Communications meet weekly to discuss results of literature and electronic database searches for sound-alike and look-alike names for proposed proprietary names. "But, just for clarification, we have a Manual of Policies and Procedures in final clearance that will define how ODS interacts with the divisions in both pre- and post-marketing settings," Phillips said.

A nationally recognized expert in medication error prevention, Phillips is an enthusiastic supporter of a proposal he and other FDA staff are working on that will require bar-coding on all prescription medicines. There will be a public meeting on the topic July 26 at the Natcher Auditorium, Building 45, on the campus of the National Institutes of Health in Bethesda.

Phillips anticipates that the proposed rule will be out in the fall. "If a unit-dose tablet was bar-coded, it could be scanned to match a bar code on the wristband of a patient," Phillips said. "Of course, the hospital would need a computer system that could verify the information. But, this rule could really reduce medication errors as medications are administered."

Phillips is aware that this may be a costly rule. "The money saved in prolonged hospitalization or premature deaths certainly would offset the costs of bar-coding," he said.

Bar-coding could also help increase the accuracy of dispensing drugs on an outpatient basis.

Phillips and his staff are also working on three guidance documents for industry that would involve FDA recommendations on:

- The process of submitting drug names to FDA.
- Labeling and packaging.
- Industry's role in evaluating a new proprietary drug name.

COUNTERTERRORISM CORNER

FDA's Counter-Terrorism Tracking System enhances collaboration

BY KAREN OLIVER

The Counter-Terrorism Programs Staff in FDA's Office of Science Coordination and Communication launched the intranet-based Counter-Terrorism Tracking System on March 11, six months after the worst terrorist attack in our country's history.

In an effort to enhance timely communication and interagency collaboration and cooperation, the tracking system is designed to be a single source for capturing all of FDA's counterterrorism activities including workload, accomplishments, planning, archiving documents and generating reports.

Your participation is essential in helping assure that the tracking system is a comprehensive account of the Agency's counterterrorism activities. We encourage the use of the system to capture all counterterrorism-related work in which you are involved.

If you are working on a counterterrorism project or activity, one of the designated CDER users with permission to input and view data will make sure the system captures your work. In CDER the contacts are:

- *Office of Counter-Terrorism and Pediatric Drug Development.* **David Cummings, Sandra Folkendt, Joanne Holmes, Brad Leissa, M.D.,** and **Christine Moser.**
- *Office of Executive Programs.* **Diane Ehrlich, Terry Martin, Jody Moore** and **Khyati Roberts.**
- *Office of Information Technology.* **Jumpol Mongkol.**
- *Office of the Center Director.* **Devota Herbert.**

The events of Sept. 11, the subsequent anthrax outbreak, and the deployment of U.S. forces in the war on terrorism have resulted in a rapid expansion of the Agency's counterterrorism efforts. In the course of meeting its counterterrorism mandate, FDA works with many agencies of federal, state and local governments; consumer groups; industry; academia; and foreign governments.

These wide-ranging activities have been coordinated centrally since the latter part of 2000 by the Counter-Terrorism Programs Staff. Working with representatives from centers and offices throughout FDA, our group serves as the FDA point of contact for all counterterrorism activities both inside and outside the Agency.

The tracking system will guide budget planning in the coming years. The current system is a pilot that will be migrated to a permanent system over the next year.

There are three different permission levels for authorized users of the tracking system. The different permission levels are viewers, users and administrators:

- Viewers have permission to view data, query the database and generate reports.
- Users have permission to input and view data, query the database and generate reports.
- Administrators have permission to input data, query the database, generate reports, and modify the system.

The Counter-Terrorism Programs Staff, under the direction of **Andrea Meyerhoff, M.D.,** has the lead responsibility for tracking system.

Within our group, **Mary Dempsey** and myself, both health science administrators, have administrative permission. We are the appropriate contacts for problems, questions, suggestions and comments about the system.

We are located in the Parklawn Building and can be reached by telephone, (301) 827-4067; fax, (301) 827-5671; and e-mail, Counterterrorism@oc.fda.gov.

Karen Oliver is a health science administrator on the Counter-Terrorism Programs Staff.

Animal efficacy data rule becomes final

FDA amended its new drug and biological product regulations so that certain human drugs and biologics that are intended to reduce or prevent serious or life-threatening conditions may be approved for marketing based on evidence of effectiveness from appropriate animal studies when human efficacy studies are not ethical or feasible.

"The terrorist attacks of last fall underscored the acute need for this new regulation," said FDA Deputy Commissioner **Lester M. Crawford, DVM, Ph.D.** "This action will help make certain essential new pharmaceutical products available much sooner—those products that because of the very nature of what they are designed to treat cannot be safely or ethically tested for effectiveness in humans."

The new rule will apply when adequate and well-controlled clinical studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers.

Under the new rule, certain new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological or nuclear substances may be approved for use in humans based on evidence of effectiveness derived only from appropriate animal studies and any additional supporting data.

Products evaluated for effectiveness under this rule will be evaluated for safety under preexisting requirements for establishing the safety of new drug and biological products.

Center's counterterror, pediatrics office moves

The Office of Counter-Terrorism and Pediatric Drug Development, formerly the Office of Pediatric Drug Development and Program Initiatives (Sept.-Oct. *Pike),* has moved from the Office of New Drugs to the Office of the Center Director. It now includes a Division of Counter-Terrorism and a Division of Pediatric Drug Development.

To ensure consistency, review divisions will send a consult to the Division of Counter-Terrorism when a drug development activity involves either an agent on the CDC's list of possible terrorists agents or a product is sponsored by the military.

The office has relocated to the Parklawn Building, Room 5A-33.

Guidance follows Supreme Court ruling on speech restrictions

FDA issued a guidance on pharmacy compounding on June 5, just over a month after the Supreme Court issued its decision in a case involving a First Amendment challenge to section 503A of the Federal Food, Drug, and Cosmetic Act. That section exempted drugs compounded by pharmacies from the law's requirements for new drug approval, adequate directions for use and good manufacturing practice if specified conditions—including two restrictions on commercial speech—were met.

The restrictions included prohibitions on soliciting prescriptions for and advertising specific compounded drugs. Section 503A was added to the Act in 1997 as part of the FDA Modernization Act.

The limits on the solicitation and advertising of compounded drugs were challenged by seven compounding pharmacies as an impermissible regulation of commercial speech.

A federal district court ruled in their favor. An appeals court held that the unconstitutional restrictions on commercial speech could not be severed from the rest of the section. It ruled the pharmacy compounding section invalid in its entirety. The government appealed to the Supreme Court, which agreed with the lower courts.

The new guidance, court decisions and other information are available on CDER's Web site at http://www.fda.gov/cder/pharmcomp.

FDA's action will provide immediate guidance on what types of compounding might be subject to enforcement action under current law while FDA considers the implications of the Supreme Court decision and determines how it intends to regulate pharmacy compounding in the long term.

"We recognize that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner," said **David Horowitz,** director of CDER's Office of Compliance. "This traditional activity is not the subject of the new guidance."

FDA officials believe that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing and distributing unapproved new drugs for human use in a manner clearly outside the bounds of traditional pharmacy practice. "Such establishments and their activities are the focus of this guidance," Horowitz said.

Some "pharmacies" that have sought to find shelter under and expand the scope of the exemptions applicable to traditional retail pharmacies have claimed that their manufacturing and distribution practices are only "the regular course of the practice of pharmacy." Yet, the practices of many of these entities seem far more consistent with those of drug manufacturers and wholesalers than with those of retail pharmacies.

For example, some firms receive and use large quantities of bulk drug substances to manufacture large quantities of unapproved drug products in advance of receiving a valid prescription for them. Moreover, some firms sell to physicians and patients with whom they have only a remote professional relationship.

Pharmacies engaged in activities analogous to manufacturing and distributing drugs for human use may be held to the same provisions of the Act as manufacturers, according to the new guidance.

"Preserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest," Associate Justice Sandra Day O'Connor wrote in the high court's majority opinion, "and the government has every reason to want as many drugs as possible to be subject to that approval process."

However, the government erred when it tried to use the fact that a pharmacy advertises compounding "to draw a line between small-scale compounding and large-scale drug manufacturing," O'Connor wrote.

"Forbidding the advertisement of compounded drugs would affect pharmacists other than those interested in producing drugs on a large scale. It would prevent pharmacists with no interest in mass-producing medications, but who serve clienteles with special medical needs, from telling the doctors treating those clients about the alternative drugs available through compounding."

Generally, FDA officials will continue to defer to state authorities regarding less significant violations of the law related to pharmacy compounding of human drugs.

However, when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration or misbranding provisions of the law, FDA will seriously consider enforcement action.

In determining whether to initiate such an action, the Agency will consider whether the pharmacy engages in any of the following acts:

- Compounding drugs in anticipation of receiving prescriptions.
- Compounding drugs that were withdrawn or removed from the market for safety reasons. The guidance provides a list of 63 such drugs, and the list will be updated in the future.
- Failing to have an investigational new drug application for drugs compounded from bulk active ingredients that are not components of FDA approved drugs.
- Receiving, storing or using drug substances without first obtaining written assurance that each lot was made in an FDA-registered facility.
- Receiving, storing or using drug components not guaranteed or otherwise determined to meet official compendia requirements.
- Using commercial-scale manufacturing or testing equipment for compounding drug products.
- Compounding drugs for third parties for resale to individual patients or offering compounded drug products at wholesale to other state-licensed persons or commercial entities for resale.
- Compounding drug products that are commercially available or that are essentially copies of commercially available FDA-approved drug products.
- Failing to comply with state law regulating the practice of pharmacy.

Office of Regulatory Policy helps develop rules, release information

BY TAWNI SCHWEMER

Have you asked yourself any of the following questions?

- Whom do I contact if a CDER regulation needs to be amended or if a new regulation needs to be developed?
- How do I develop a guidance document or a MAPP?
- What kinds of drug-related information can I discuss with the public?
- Where do I turn if I have a question about user fees?
- How do I submit a document or issue for comment or clearance to the Office of Chief Counsel?
- Whom do I ask about the status of a citizen petition?
- How do I find information on a candidate for debarment?

If you have ever asked yourself one of these questions, CDER's Office of Regulatory Policy is here to help.

The former Regulatory Policy Staff and Freedom of Information Staff were combined to form the new office with **Jane Axelrad,** CDER's associate director for policy, as office director. We:

- Develop regulations and assist the Center with the development of guidance documents and MAPPs.
- Collect annual product and establishment user fees, handle user-fee waiver requests and assist the Center with questions about application user fees.
- Review drug-related documents before they are given to the public to ensure that confidential or proprietary information is not released.

We currently have 44 people working in our office, including regulatory counsels, consumer safety officers, pharmacists, writer-editors, policy analysts and several support staff. Our office has three divisions.

The Division of Information Disclosure Policy, directed by **Andrea Masciale,** prepares, develops, and coordinates Center and Agency responses to requests for drug-related documents. These requests come from the public under the Freedom of Information Act, other governmental agencies and persons in litigation who want the Agency's information to help their cause.

The division also prepares approval packages, warning letters and other documents of significant public interest for posting on the CDER Web site.

The division must ensure that all drug-related documents are processed under the law and in accordance with established FDA regulations, policies and procedures.

The other two divisions are the Divisions of Regulatory Policy I and II, directed by **David Read** and **Virginia Beakes**, respectively.

These divisions serve as the Center's focal point on regulatory issues. They provide advice and assistance on such matters as scope, applicability and interpretation of the Food, Drug and Cosmetic Act and other laws, regulations and policies.

People in these divisions have a number of responsibilities, including drafting regulations and guidances, reviewing MAPPS, responding to citizen petitions, handling debarment issues and coordinating the clearance process for these documents.

To give you an idea of our workload, here are some interesting statistics:

- On behalf of CDER, we collected about $100 million in annual product and establishment fees for fiscal year 2002.
- Each year, we assist the Center with issuing approximately 50 guidance documents.
- In 2001, we received 47 new citizen petitions.
- During 2001, we published one direct final rule, four final rules, three proposed rules and one interim rule in the *Federal Register*.
- In any given month, we receive about 600 new Freedom of Information Act requests.
- This past year, we released to the public, in litigation and on the CDER Web site, almost 10,000 pages about the approval of mifepristone.

Here is a list of some or our MAPPs that you may find helpful:

- *Submitting Proposals to the Office of Regulatory Policy for Early Analysis of Rulemaking Initiatives*, MAPP 4000.3, explains what you need to do if you are planning to develop a proposed regulation.
- *Developing and Issuing Guidance for Industry*, MAPP 4000.2, describes the guidance development process.
- *Guide to Issuance of Directives in CDER*, MAPP 4000.1, describes in detail how MAPPs are developed and cleared.
- *Submitting Issues/Documents to the Office of the Chief Counsel for Legal Review/Comment or Clearance*, MAPP 4140.5, describes the process for submitting CDER documents or issues to the Office of Chief Counsel for review or clearance.
- *Submitting Non-FOIA Requests for Document Collection and Redaction to CDER's Division of Information* Disclosure *Policy*, MAPP 4170.2, describes the process for submitting non-FOIA requests to DIDP.
- *Repository Searching in the Division of Information Disclosure Policy*, MAPP 4170.5, describes how DIDP can search the Agency's FOI database for pertinent information relating to FOIA requests.

In addition, we maintain the following intranet and World Wide Web sites:

- http://cdernet.cder.fda.gov/orp has information about our office, lists contact phone numbers and has useful links to the MAPPs listed above.
- http://cdernet.cder.fda.gov/guidancedoc/gsquaredindex.htm contains information on guidance and MAPP development and the guidance repository.
- http://www.fda.gov/cder/fdama contains a list of all documents issued by CDER under the FDA Modernization Act of 1997.
- http://www.fda.gov/cder/guidance/index.htm contains a list of current guidances and other lists generated to meet Good Guidance Practice regulations.
- http://www.fda.gov/cder/MAPP.htm contains a list of all current MAPPs.
- http://www.fda.gov/cder/pdufa/default.htm contains useful information on user fees under the Prescription Drug User Fee Act.

Tawni Schwemer is a policy analyst in ORP's Division of Regulatory Policy II.

Center, industry, consumer groups promote OTC Drug Facts label

By Mandy Eisemann

May 16 marked the date that most of the more than 100,000 over-the-counter drug products were required to display the new easier-to-read Drug Facts label on their products.

The FDA rule, finalized in 1999, requires a standardized format for the labeling of the drugs Americans use most often—OTC drugs.

Even before the official implementation date, many manufacturers had voluntarily adapted the new label. In recent surveys, randomly selected categories of OTC drugs at a retail chain showed that nearly 75 percent of labels examined already displayed the Drug Facts label.

FDA has been cooperating on publicizing the new label with a patient group, the National Council for Patient Information and Education, and an OTC trade group, the Consumer Health Care Products Association.

Public awareness efforts included press conferences in Washington and New York City, press releases, a consumer brochure, posters in the Washington Metro system and public service announcements.

The consumer information brochure, jointly produced with CHPA, is called "The New Over-the-Counter Medicine Label . . . Take a Look!" The educational guide was developed to promote awareness and provide helpful information on why the new Drug Facts label is even easier to read and understand.

The pamphlet highlights for consumers the importance of reading and following the directions on an OTC product's label. It includes an illustration of what the new Drug Facts label looks like, and also a section describing the use of tamper-evident packaging as an added safety feature in OTC medicine packaging.

"Our overall goal is to ensure that consumers are encouraged to read product labels carefully," said FDA Deputy Commissioner **Lester M. Crawford, DVM, Ph.D.** "Reading the new label will help consumers choose an appropriate over-the-counter product for their symptoms, and it will also help them avoid complications by using the product correctly."

CDER speakers at the May event were **Jonca Bull, M.D.,** the director of the Office of Drug Evaluation V; **Linda Katz, M.D.,** the deputy director of the Office of Over the Counter Drug Products; and **Ellen Shapiro,** the director of the Division of Public Affairs in OTCOM.

Special thanks also go to **Cazimerio Martin, M.D.,** DOTCDP; **Sharan Jayne** and **Laura Bradbard,** FDA Office of Public Affairs; and **Bill McConagah,** FDA Office of Chief Counsel.

You can find HTML and PDF versions of the consumer pamphlet on our Web site at http://www.fda.gov/cder/consumerinfo/OTClabel.htm. We have a supply of printed copies, so e-mail me (EISEMANNM) if you would like some.

Mandy Eisemann is a public affairs specialist in OTCOM's DPA.

Project Management Corner

PM Communications Committee EXPANDs

By Diane Moore and Virginia Yoerg

The Project Management Communications Committee has been busy keeping the communication lines open. Project managers can ask questions or make suggestions to the committee by sending their messages to the e-mail account PMEMAIL.

Updates of upcoming meetings, workshops and seminars are now being sent to CDER's project managers on a monthly basis. The committee also has subcommittees that work on projects such as the PM Web page and the PM Resource Manual, both of which are at http://cdernet.cder.fda.gov/pmcc/default.htm.

The Committee would like to announce its launch of the EXPAND program (EXploring Project Management Activities iN Drugs). This project management shadowing program was established in CDER to foster interdivisional mentoring. The pilot program is underway with three teams of project managers working together to share their expertise between respective divisions. If you are interested in participating in EXPAND, please send an e-mail with your name to the PMEMAIL account.

There is room for growth on the our committee for energetic individuals. We are recruiting for at least one representative from each CDER office.

If you're interested, send an e-mail to the PMEMAIL account.

Diane Moore and Virginia Yoerg are the committee's co-chairs and regulatory health project managers in the Divisions of GastroIntestinal Drug Products and Anti-Viral Drug Products respectively.

Firm signs consent, agrees to record $500 million fine

FDA announced on May 17 that Schering-Plough Corp., its subsidiary Schering-Plough Products, LLC, and two principal corporate officers have signed a consent decree of permanent injunction agreeing to measures to assure that the drug products manufactured at the firms' New Jersey and Puerto Rico plants are made in compliance with FDA's current good manufacturing practice regulations. The firms will pay a record $500 million, the highest monetary settlement in FDA history.

The government's action in this case followed 13 inspections at four New Jersey and Puerto Rico facilities since 1998 during which FDA found significant violations of the CGMP regulations related to facilities, manufacturing, quality assurance, equipment, laboratories and packaging and labeling.

"This action is another clear sign that FDA will continue to enforce the rules and regulations requiring companies to carefully control and monitor their processes used to make pharmaceuticals and other products, so that those products will be safe and effective," said FDA Deputy Commissioner **Lester M. Crawford, DVM, Ph.D.** "Manufacturers who choose to wait until FDA investigators find violations rather than policing themselves will find that they have made a poor and costly decision."

Harvard award recognizes Dr. O'Neill's biostatistics contributions

The Department of Biostatistics at the Harvard School of Public Health in Boston on May 31 presented its annual Marvin Zelen Leadership Award in Statistical Science to **Robert O'Neill, Ph.D.,** director of the Office of Biostatistics.

"This award is a big deal," said **Susan Ellenberg, Ph.D.,** Director, Office of Biostatistics and Epidemiology at the Center for Biologics Evaluation and Research. "All the others who have received it are extremely senior academic statisticians. Bob is the first primarily applied person to receive this honor. His wife and son were there, too. Many FDAers, including **Bob Temple, Mo Huque, Chuck Anello** and **Jim Hung** from CDER, myself and **Jay Siegel** from CBER, and **Greg Campbell** from CDRH, were at the meeting, and we were all extremely proud to see Bob get this award."

The annual award recognizes an individual in government, industry, or academia, who by virtue of his or her outstanding leadership, has greatly impacted the theory and practice of statistical science.

Steven Lagakos, Ph.D., the chair of the Department of Biostatistics, who introduced Dr. O'Neill, noted that in the early 1970s he was advised not to seek employment at FDA "because statisticians were not valued there and most of the work that statisticians did was not very influential or sophisticated."

He noted that a strong and influential part of today's FDA is statistical thinking and the use of modern statistical methods to evaluate clinical trials and other studies. Among the many causes for the change, Dr. Lagakos cited Dr. O'Neill's major impact in convincing FDA leadership about the importance of study design and monitoring, about the use of current and efficient methods in the interpretation of study results, and about the need for the FDA to remain current in the many developments in the statistical profession.

"What Bob has done is far more than recognizing that the mission of FDA would be enhanced if statistics played a more prominent role," Dr. Lagakos said. "He actually was able to help to modify the institution by having these views implemented. Indeed, I firmly believe that the evolution of thought, practice and quantitative expertise within the FDA would not have occurred nearly as much as it has without Bob's leadership."

Dr. O'Neill's lecture, "A Perspective on the Development and Future of Statistics at the FDA," discussed how the statistical program at CDER has been influenced and shaped over the last 30 years. The most important influence he cited were the evidence-based regulations, which created the foundation for the growth of statistical science and stimulated its development. Beginning in 1970 with the definition of "adequate and well-controlled studies," FDA slowly established the process, principles and written documentation to carry out the statistical evaluation of evidence submitted by the pharmaceutical industry, Dr. O'Neill said.

The environment for implementation of newer statistical methods, study designs and efficiencies in study designs became an accepted part of the drug development and review process, Dr. O'Neill said. Challenging unsolved problems in clinical trials and in non-clinical and related areas drove FDA statisticians to assume a greater role in regulatory research.

Dr. O'Neill also noted that globalization of drug development opened the opportunity for internationally developed statistical guidelines for clinical trials; greater visibility and understanding of the central role that statistical planning, design, analysis and interpretation play in the drug development process; and the multidisciplinary involvement necessary for successful drug development.

Dr. O'Neill's lecture can be found in Recent Presentations on OB's intranet at http://cdernet.cder.fda.gov/ob/index.htm.

Award for Dr. Szarfman

Ana Szarfman, M.D., from the Quantitative Methods and Research Staff in the Office of Biostatistics, was awarded the 2002 FDA Scientific Achievement Award for Outstanding Intercenter Scientific Collaboration at the FDA Science Forum held earlier this year. The citation is "for outstanding collaboration for development and implementation of a scientific and sophisticated signal surveillance system to identify potential safety concerns for medical products." Over the last five years, she has created a datamining system for automatic screening of the FDA adverse events data bases and software for visualization and analysis of signals.

Pike's Puzzler: What was on that label?

BY TONY CHITE

1. Extended-release tablets should be:

a. Dissolved in water in the spoon but not in a glass of water.
b. Swallowed whole and should not be broken or chewed.
c. Crushed and placed in applesauce if patient is unable to swallow a tablet.
d. Completely dissolved in the mouth and swallowed slowly.

2. USP controlled room temperature for storage of a drug is:

a. 68-77 degrees Fahrenheit.
b. 58-67 degrees Fahrenheit.
c. 78-79 degrees Fahrenheit.
d. 60-63 degrees Fahrenheit.

3. What information is usually not found on the label of the box or package of a prescription drug?

a. Expiration date.
b. Lot number.
c. Manufacturer.
d. Storage conditions or temperature range.
e. None of these.

4. The NDC number on a drug label:

a. Is the National Drug Code.
b. Contains a code that indicates manufacturer of the drug.
c. Contains a code number that indicates the package size.
d. All of these.
e. a and b only.

Key: 1b; 2a; 3e; 4d

Tony Chite is a pharmacist and consumer safety officer with the Division of Information Disclosure.

PQRI's first recommendations focus on blend uniformity

The Product Quality Research Institute forwarded its first recommendation to the Center for review in March. The recommendation proposes that in-process dosage unit analysis be considered as an alternative to routine blend sampling analysis to satisfy the Agency's good manufacturing practices requirement to demonstrate "adequacy of mixing to assure uniformity and homogeneity." The recommendation would apply to tablet cores, hard gelatin capsules or other solid dosage forms.

Shortly after receiving the institute's report, FDA announced that it was withdrawing a controversial 1999 draft guidance on blend sampling.

PQRI brings together for the first time the innovator and generic pharmaceutical industry, academia and CDER to address issues related to pharmaceutical product quality.

The recommendation, "The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends," represents an extensive effort by PQRI's Blend Uniformity Working Group to address the gap between scientific principles and regulatory policy related to blend uniformity analysis and content uniformity of solid oral dosage forms.

The working group process included:

- Identification of the issues associated with blend uniformity analysis as currently performed in which powder blends are sampled and analyzed before manufacture of the final oral dosage form.
- Evaluation of the scientific literature on the topic of blend uniformity.
- Careful evaluation of various alternatives to blend analysis.

According to PQRI, the recommendation has many positive aspects, including:

- Providing an accurate and reflective measure of the homogeneity of a product.
- Eliminating blend sampling errors.
- Applying resources where they produce reliable, accurate information about the quality of the product given to the patient.
- Eliminating the weighing errors associated with blend sampling.
- Removing the safety issues surrounding blend sampling of toxic or potent drugs.
- Accounting for segregation after blending.

In an agreement between FDA and PQRI, the Agency will evaluate the recommendation and either adopt it or, if it chooses not to adopt it, provide a scientific explanation to PQRI where the recommendation is lacking.

In addition to academic and industry members, the PQRI's Blend Uniformity Working Group included CDER representatives from the Office of New Drug Chemistry, the Office of Generic Drugs and the Office of Compliance. Several other working groups are in the process of conducting research to provide scientific evidence for assisting FDA in evaluating its policies and guidances.

For more information on PQRI, visit http://www.pqri.org.

OPS launches Rapid Response Team to resolve scientific brushfires

BY PATRICK E. CLARKE

As part of the reengineering of the Office of Testing and Research, the Office of Pharmaceutical Sciences created the Rapid Response Team to link OTR's laboratories more directly with review activities. The team works directly under OPS to provide it with more visibility and access to scientific issues.

Led by **Nakissa Sadrieh Ph.D.,** the Rapid Response Team, is a multidisciplinary unit of scientists who design and oversee expedited research projects to address specific questions and to facilitate science-based regulatory decision making.

"This is FDA's way of adapting to changing needs," Dr. Sadrieh said. "Regulatory people have to make faster and faster decisions, so there's a need to respond to issues more quickly. Expanded studies have a very important place, the team just complements ongoing research and directly impacts regulatory decisions. We'll be responding to applied science questions—we won't be winning any Nobel Prizes."

The team has already responded to a number of urgent regulatory issues.

Recently, a study of the palatability of the antibiotic doxycycline was concluded. The CDC's National Pharmaceutical Stockpile Program had only solid dosage forms of the drug. "There is no liquid version of doxycycline in the stockpile that can be given to children," Dr. Sadrieh said. "So, the issue was whether the available tablets could be dissolved into milk or applesauce to make the drug palatable to children."

Under the watchful eye of the response team, volunteers from FDA took doxycycline with milk, syrup and other substances. The whole project from start to finish took less than three months. "Now, the regulatory people will decide the outcome," Dr. Sadrieh said.

A division could ask the Rapid Response Team to find specific answers before a drug is approved. "We have lab facilities, a budget and will be interacting with industry and academia," Dr. Sadrieh said. The team can even contract for certain projects if necessary.

Dr. Sadrieh is working on a one-page format for divisions to submit with their proposals. The team will ask for simple proposals, with important potential consequences. "Our research might affect whether a black box warning is added to a drug label or our input might affect some other aspect of labeling, or lead to a recall," Dr. Sadrieh said.

Currently, the team consists of the leadership within the Office of Testing and Research. The other team members are: **Robbe Lyon, Ph.D.,** deputy director of the Division of Product Quality Research; **Joseph P. Hanig, Ph.D.,** deputy director of the Division of Applied Pharmacology Research; **John H. Strong, Ph.D.,** deputy director of the Laboratory of Clinical Pharmacology and **Moheb M. Nasr, Ph.D.,** acting director of the Office and Testing and Research.

Membership will be expanded so that all the disciplines covered by OPS will be represented.

OPS forms advisory group for process analytical technologies

In an effort to obtain ongoing expert advice on process analytical technologies (see page 1), the Office of Pharmaceutical Science has formed a new subcommittee of the Advisory Committee for Pharmaceutical Science: the Process Analytical Technologies Subcommittee.

At it first meeting in February, **Ajaz Hussain, Ph.D.,** OPS deputy director, provided the group an overview and outlined FDA's plan to facilitate the introduction of new production technology by eliminating regulatory uncertainty.

The February meeting brought together more than 60 experts in the areas of analytical chemistry, physical chemistry, pharmaceutical technology, regulatory compliance, chemical engineering and international pharmaceutical manufacturing. (A second subcommittee meeting was held in June.)

Experts from both the innovator and generic industries and from academia joined experts from OPS, FDA's Office of Regulatory Affairs and CDER's Office of Compliance.

Dr. Hussain chairs the FDA's PAT steering committee and is joined by **Douglas Ellsworth,** New Jersey district director; **Michael Olson, Ph.D.,** ORA; **Joseph Famulare,** Office of Compliance; and **Frank Holcombe, Ph.D., Moheb Nasr, Ph.D.,** and **Yuan-yuan Chiu, Ph.D.**, from OPS.

Four working groups will cover the following topics:

- Process analytical technologies, applications and benefits.
- Chemometrics.
- Product and process development.
- Process and analytical validation.

FDA plans a general guidance on PAT accompanied by workshops and training. CDER has invited companies to propose submissions, which are expected later this year. An e-mail account (PAT@cder.fda.gov) has been set up to facilitate communication. An intranet site (http://cdernet.cder.fda.gov/ops/pat) has more information including panel membership, meeting transcripts and presentations.

PDUFA III maintains review goals, supports some post-market surveillance

(Continued from page 1)

Under PDUFA II, FDA collected significantly less in user fees than estimated due to a reduced number of new drug applications and an increased proportion of submissions whose fees were waived.

The law puts the user fee program on a sound financial basis by authorizing FDA to collect $1.2 billion in user fees over the next five years. This will enable the Agency to increase the staffing of the drug and biologics review programs by 450 full-time employees and improve their working conditions and training.

FDA is also concerned about the safety of new medicines following approval. In recent years, fully 50 percent of all new drugs worldwide have been launched in the United States, and American patients have had access to 78 percent of the world's new drugs within the first year of their introduction.

The law authorizes FDA to spend $70 million of user fees to increase surveillance of the safety of medicines during their first two years on the market or three years for potentially dangerous medications. It is during this initial period, when new medicines enter into wide use, that FDA is best able to identify and counter adverse side effects that did not appear during the clinical trials.

"PDUFA will be stronger and more effective than ever," said FDA Deputy Commissioner **Lester M. Crawford, DVM, Ph.D.** "With the additional resources and an enhanced ability to monitor safety of new drugs as they enter the marketplace we're taking a step forward in transforming FDA into an even more efficient agency, while maintaining our high standards of safety."

Alosetron returns to market with risk management program

FDA announced on June 7 the approval of a supplemental new drug application that permits marketing of alosetron hydrochloride (Lotronex) with restrictions. The manufacturer of the drug, GlaxoSmithKline, will be implementing a risk management program including a prescribing program to enroll physicians who wish to prescribe Lotronex.

The drug's indication has been narrowed to be only for treatment of women with severe, diarrhea-predominant irritable bowel syndrome who have failed to respond to conventional IBS therapy. Limiting the use of alosetron to this severely affected population is intended to maximize the benefit-to-risk ratio.

The marketing of alosetron is being restricted because serious and unpredictable gastrointestinal adverse events, including some that resulted in death, were reported in association with its use.

FDA first approved alosetron in February 2000, and it was voluntarily withdrawn in November 2000. More information is at http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm.

Study examined patient information with Rx medicines

(Continued from page 1)

The scores for individual criteria varied, with the highest scores (greater than 90 percent) showing that the information distributed was scientifically accurate, up-to-date and non-promotional.

A 1996 law requires HHS to evaluate the adequacy of private sector prescription drug information given to patients. The goal contained in that law was that 75 percent of patients obtaining new prescriptions by the year 2000 were to receive useful written information.

Because FDA sees progress in achieving distribution targets, the Agency will continue to work with private sector partners to improve the usefulness of patient information and meet the goal for the year 2006, which calls for 95 percent of patients obtaining new prescriptions to receive useful written medication information at the time of dispensing.

CDER aims to foster use of new drug manufacturing technology

(Continued from page 1)

sensors is able to look at everything—not only active ingredients but also inactive ingredients the distribution of moisture within a product. The combination of signals from these sensors gives rise to the identity of and information about individual components.

A mathematical, computer-based model would analyze the signals and provide the information about the individual components. With PAT these measurements can be made in real time and online. While the laser and infrared technology is available now, much scientific work remains to be done to integrate them into drug manufacturing. Computer models must be designed and validated to show that they accurately and consistently report the nature of the chemicals in the process.

Quality control using PAT is based on real-time electronic data rather than paper documentation. PAT thus holds the promise of simultaneously notifying both the manufacturing and the regulator of quality problems.

Continuously monitoring drug processing could dramatically reduce the time needed to get a drug to market. On average, it takes 60 to 90 days to manufacture and release a batch of tablets to market, according to data from G.K. Raju, Ph.D., executive director of the Pharmaceutical Manufacturing Initiative at the Massachusetts Institute of Technology. When there are deviations from standards, the cycle time is greatly increased.

"The new methods can result in a 10-fold decrease in cycle time," Dr. Raju said, "because everything is on line."

Consensus building

Making PAT a reality will require careful planning and consensus building. "Our first step has been to bring this idea into public awareness and build consensus," Hussain said.

Steps taken by the Office of Pharmaceutical Science have included:

- Presenting the concept to the Advisory Committee on Pharmaceutical Science last July.
- Coordinating with the Office of Compliance and FDA's Office of Regulatory Affairs.
- Gaining endorsement of the concept from the FDA's Science Board at its meeting in November.
- Introducing the concept to the Center in scientific rounds.
- Establishing a Process Analytical Technology Subcommittee with four working groups under the aegis of the Advisory Committee on Pharmaceutical Science.
- Setting up a PAT lecture series during April in cooperation with the Office of Training and Communications.

The lecture series was developed to provide the CDER's scientists with a basic background in PAT. The lectures should help the Center develop an appropriate regulatory framework for possible PAT implementation. The lectures were videotaped and are available through the FDA Medical Library.

Regulatory challenges

The Center has been aware of scientific advances in the area of PAT for several years. "Many of the PAT tools have been in use in other chemical industries," Hussain said. "This experience provides a means for assessing their reliability in day-to-day operations and potential for applications in pharmaceutical manufacturing. You often need a higher level of reliability for pharmaceuticals."

The pharmaceutical industry tends to stay with established technologies and systems, in part because of a perceived risk of regulatory uncertainty regarding new technologies.

Inefficiencies in current drug manufacturing practices were brought to light during a presentation to the FDA Science Board from PriceWaterhouse Coopers Consulting. Their study found that it is common for the pharmaceutical industry to plan for 5 percent to 10 percent of their batches to be scraped and reworked. Actual failure rates, however, may be higher.

Moving forward

A PAT steering committee will oversee the development of a draft guidance to industry, which is expected to be ready by the end of August. In addition, CDER has invited industry to propose submissions using PAT technologies. Two companies have indicated they are interested in discussing their proposed submissions.

Members of the steering committee are: **Douglas Ellsworth**, who heads FDA's New Jersey District Office; **Mike Olson, Ph.D.,** from FDA's Office of Regulatory Affairs; **Joseph Famulare,** director of the Division of Manufacturing and Product Quality in the Office of Compliance; **Moheb Nasr, Ph.D.,** from the Office of Testing and Research in OPS; **Frank Holcomb, Ph.D.,** Office of Generic Drugs in OPS; **Yuan-yuan Chiu, Ph.D.,** director of the Office of New Drug Chemistry in OPS. Dr. Hussain is chairing the committee.

Already there are pharmaceutical manufacturing plants in Germany and Australia using various levels of the PAT process. "Although there are some plants in Germany using the process, I think the common understanding of PAT standards are uncertain throughout Europe at this point," Dr. Hussain said. "I anticipate that we will be able to define rigorous scientific standards quickly through the subcommittee process."

Dr. Woodcock said she sees two challenges facing the FDA regarding PAT. "I see our challenges as articulating guidances and addressing existing but 'hidden' problems in the current process that may surface as new technologies are introduced," she said.

The idea that using PAT will uncover problems was put in perspective by **David Horowitz**, the director of CDER's Office of Compliance. "We'll also find more solutions to problems, which will preclude regulatory action," he said.

Another challenge for CDER will be to recruit and train a scientific workforce proficient in the new technologies. Dr. Hussain envisions an interdisciplinary program with at least four areas: pharmaceutics, analytical chemistry, chemical engineering and information science.

Dr. Hussain said CDER needs to move PAT forward to counter industry perceptions that regulation is a roadblock. "I'd like to see us become the leaders in the application of this technology to improve the efficiency and quality of drug manufacturing processes," Dr. Hussain said.

Patrick Clarke is a public affairs specialist in OTCOM.