news along the pike

Center for Drug Evaluation and Research

December 1997

Volume 3, Issue 12

Inside . . .

Pike's Corners . . .

Sweeping Changes Now Law

Clinton Says FDA Wins "Gold Medal"

By Nancy Derr

On Nov. 21, the marathon FDA legislative effort finally reached its end. In signing the FDA Modernization Act of 1997 into law, President Clinton praised the FDA's effort, saying the Agency had won a "gold medal for leading the way into the future." The President thanked all of those who took part in the three-year legislative effort. He described the act as "astonishing work" that passed in both Houses by a voice vote. Many members of the CDER staff played a role in helping to craft the final legislation. The commitment of the Center's leadership, especially **Janet Woodcock, Jane Axelrad** and **Mac Lumpkin,** was reflected by hours and hours of work, at almost any time of the day or night, in making sure that the legislation reflects CDER's goals.

The act contains some of the most sweeping changes to the Food, Drug, and Cosmetic Act in 35 years. It codifies many of FDA's reinventing government initiatives and other existing programs.

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Safety Committee Initiative

First Responders Help Accident Victims

By Pam Fagelson

First aid training, sponsored by the Center's Occupational Health and Safety Committee to make CDER's far-flung work sites safer, found its first use in the community. **Kathy Abel,** the Office of Clinical Pharmacology and Biopharmaceutics, and **Gregg Davis,** Office of Generic Drugs, used their training to help victims in two separate highway accidents. Abel and Davis were graduates of the initial class of First Responder students. During the course they had learned how to render basic levels of first aid, assess and triage accident victims and establish accident scene control until a higher level of care arrives.

One evening, Kathy was pulling into her driveway when she heard an accident nearby. She sent her son to call 911. At the scene, she found a single car with a very shaken-up driver. Calling to mind the ABCs of her training, a "very nervous" Kathy identified herself and determined that the driver appeared uninjured. However, Kathy noticed that the car seat was

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Satellite Broadcast

Update Provided on Adverse Event Reporting

By Norman Oliver

Forty pharmaceutical firms were on-line, either through a video or audio link, to a two and one-half hour live conversation Nov. 19 about the Center's efforts to build a world-class safety surveillance system for drugs. Two panels of CDER experts, moderated by Office of Training and Communications (OTCOM) Director **Lucy Rose,** discussed the new regulatory and technological framework for adverse event reporting. Presented in TV-talk-show style, the event featured call-in and fax-in questions from the industry viewers. The show was produced in partnership with the Food and Drug Law Institute (FDLI) and was broadcast by satellite from the Gaithersburg television facility of the Center for Devices and Radiological Health (CDRH).

One aspect of the Adverse Event Reporting System (AERS) (see April *Pike*) represents a fundamental shift in the way industry and the Center conduct drug safety monitoring. Currently, industry sends CDER hard copies of

(Continued on page 6)

Joe's Notebook

Pike Salutes 85 Authors in 1997

Another year of the *News Along the Pike* draws to a close. As you make the rounds of office parties this holiday season, please join me in thanking as many as you can find of the 85 authors who made the *Pike* possible. None of these people, your friends, co-workers and colleagues, had to write for the *Pike*. All took the time out of busy schedules to share with the rest of you some item that may have made your work easier, helped you understand more about the CDER community or informed you about some unknown aspect of the Center's activities. No one has to write for the *Pike*, all volunteered the talents and efforts for you.

So, here are the 1997 *Pike* authors:

Russ Abbott, Kathleen Alt, Tim Ames, Carol Assouad, Jane Axelrad, Jackie Barber, James B. Baughman, Margaret Bell, Greg Boland, Linda Brophy, Paul Brown, Laurie B. Burke, Heather A. Chafin, Wendy Cheng, Charlene Cherry, Ruth Clements, Sarah Coburn, Bronwyn Collier, June Cory, Kristin Crown, Rose Cunningham, Susan Cusack, Nancy Derr, John Emelio, Pam Fagelson, Zan Fleming and **Karl Flora.**

Noreen Gomez, Noreen Gomez, Mark Gonitzke, David Graham, Lanh Green, Roger Gregorio, Stephen Hayleck, William A. Hess, Carolann Hooton, Ajaz Hussain, David Isom, Betty L. Jones, Deborah Kallgren, David B. Katague, Lydia Kaus, David Kausal, Joyce Korvick, Mary E. Kremzner, Ivy F. Kupec, Mary Lambert and **Karen Lechter.**

Murray Lumpkin, Sue Makoff, Debbie McKemey, Edward Miracco, Jim Morrison, Toni Nearing, Janice Newcomb, Sally Newman, Carol Norwood, Karen Oliver, Nancy M. Ostrove, Raye Parker, Lana Pauls, L. Miriam Pina, Victor Raczkowski, Khyati Roberts, Rosemary Roberts, Kathy Robie-Suh, Kevin Ropp, Lucy Rose and **C.D. "Russ" Rutledge.**

Eric Sheinin, Kassandra Sherrod, Ted Sherwood, Diane Smith, Nancy Smith, Doug Sporn, Gloria Marquez Sundaresan, John Swann, Sarah Thomas, Rich Vengazo, Grant Williams, Roger Williams, Pam Winbourne, Janet Woodcock, Jean A. Yager, and **Angie Youngblood.**

There are many unsung heroes and heroines who also made the *Pike* possible this year. During my two-month "vacation" from my editorial duties, **Lori Frederick** and others pitched in to bring you two issues. Lori, **Laura Bradbard, Elaine Frost, Lucy Rose, Tony Sims, Ellen Shapiro, Marcia Trenter** and **Pam Winbourne** in OTCOM all helped me squash typos, check facts and otherwise ensure the *Pike* is as accurate as we can make it.

A host of others, some known to me and others toiling anonymously, contributed to bringing you the *Pike*. Some helped with research or writing, some took time to check facts and review stories and others helped make photocopies.

Finally, a happy holiday to the most important people to the *Pike*—you, its readers.

I've been asked why there are no pictures in the *Pike*. For those of you reading a photocopy of the *Pike*, the answer is: photocopying. Photographs reproduce terribly, even more so when its a second- or third-generation photocopy. For those of you who make a printout, the answer is: peace in the office. Most of us are hooked up to network printers, and photos take forever to print. For those of you happy to read the *Pike* on-line, there are no drawbacks to photographs. They appear in all their glorious colors. The *Pike's* holiday gift to you is a photo supplement. Click in the box on page 6. So send in your photos or e-mail the scans. Happy holidays!

news along the pike

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

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Ombudsman's Corner

What You Say—Part II

By Jim Morrison

In my last column, I discussed two significant hindrances to communication with the regulated industry: not keeping applicants informed of the progress of their applications, and slowness or unwillingness to set up meetings. This month, I'll give you more examples of problems in communication I've seen in CDER.

Many new reviewers do not appreciate the havoc that ensues from a casual request for more information in an application. In the New Reviewers Workshop session on industry interactions, we bring in a representative of the pharmaceutical industry to address and dialogue with the participants. Most of them have stories to recount about CDER requests that caused some real headaches.

There is a fine line between following guidances for the sake of consistency and blindly insisting that the methods suggested in guidances be followed . . .

In general, companies treat each request seriously. If it is easy to provide, there is never any hesitation about answering your questions. However, if it entails additional work to answer, the company has to decide whether the requested data are reasonable, how much it will cost to provide the information, and how long it will delay the process. Unless it is onerous and time-consuming and clearly unwarranted by the review requirements, most firms won't balk. I have heard of questions that took several hundred thousand dollars and several months to answer, but the applicant complied, even when the basis for the request was not clear or when the information was not viewed as useful in evaluating the safety or effectiveness of the product. My advice is always to be careful about what you ask for, how you describe it and to clear even minor requests through supervisors.

Nothing enrages applicants more or destroys our credibility faster than a request that is viewed as arbitrary and motivated by personal interest rather than as necessary for establishing the safety and effectiveness of the product. Even legitimate questions or requests for additional data, if the reasons for them are not clearly stated, can appear arbitrary and capricious. Please remember that the Administrative Procedures Act prohibits government actions that are arbitrary and capricious.

The best way to avoid the appearance of asking for information out of personal interest or intellectual curiosity is to publish a guidance that informs everyone of our requirements and the bases for them. But slavish adherence to a guidance that does not make sense in a particular case will absolutely drive applicants crazy. There is a fine line between following guidances for the sake of consistency and blindly insisting that the methods suggested in guidances be followed, even when the applicant prefers to use an equally valid alternative method. Guidances are recommendations, not requirements. Of course, alternatives suggested by the applicant should be reasonable, valid and appropriate.

Old habits are hard to break. Before PDUFA, it was fairly common for CDER staff to explain delays to applicants in terms of a lack of resources. Such explanations seemed reasonable when meetings were held in small conference rooms with distressed tables and an eclectic array of ugly chairs. But times have changed. Particularly when dealing with applicants covered under PDUFA, explaining that a lack of resources is delaying an application, even if true, is not well received. No one believes the government doesn't have enough money, especially representatives of a company that just forked over $200,000 in user fees. So keep your credibility and swallow those excuses about a lack of resources before you utter them.

I'll give you the last three of my top eight problems with communications in an upcoming column. In the meantime, have a great holiday season.

Jim Morrison is the Center's Ombudsman.

Division of Training and Development to Announce Spring Courses

By Debbie McKemey

In just a few weeks the new CDER training course schedule for the spring will be published. This represents a great opportunity for you to learn new skills, refresh old ones or improve your work performance. In addition to our usual lineup of courses offered through the Staff College, New Reviewer Training and the CDER Career Skills Program, two new seminars have been developed for the Leadership and Management Development Curriculum.

These new courses, Introduction to Leadership and Selection Interviewing are one-day seminars intended for present and potential supervisors, managers and team leaders.

- The *Introduction to Leadership* seminar will serve as a basis for all management and leadership courses. It will introduce new skills that will enhance the way you lead.
- The *Selection Interviewing* seminar will give you a step-to-step guide to hiring the right people for your positions. You will learn various strategies that in the long run will improve productivity of your staff.

The Distance Learning Satellite Program promises great new programs from the National Institutes of Health, Centers for Disease Control and Prevention and the American Society of Training and Development.

Stay turned to CDERNET for your on-line schedule of classes as well as an updated list of materials available in our Learning Resource Center.

For additional information, please contact the OTCOM's Division of Training and Development at 7-4580.

Debbie McKemey is a training specialist in OTCOM's Division of Training and Development.

Information Technology Corner

OIT Designs Pediatric Labeling Tracking System

By Sally Newman

The Division of Applications Development Services (DADS) has developed and implemented an electronic system, the Pediatric Labeling Tracking System, to track supplements submitted under the 1994 Pediatric Rule more efficiently. To do this, DADS worked with other divisions in Office of Information Technology (OIT) and Office of Review Management (ORM).

In Dec. 1994, FDA published the final rule on revision of the "Pediatric Use" subsection in the labeling. This rule applies to human prescription drug products and recognizes several methods to establish evidence in support of pediatric labeling claims, including relying on efficacy established in studies carried out in adults when the disease or condition being treated is sufficiently similar in the pediatric and adult populations. Moreover, the rule requires sponsors to reexamine existing data to determine whether the Pediatric Use subsection of the labeling could be modified and, if so, submit a supplemental application.

To track the supplements submitted under this rule, a working group of the Pediatric Subcommittee with members from OIT and ORM developed the CDER Pediatric Use Supplement Form. Using this paper-based form, consumer safety officers and project managers have been providing their document rooms with pediatric rule information.

The electronic system features an Oracle Forms 4.5 graphical user interface data entry form. The form allows the division document rooms to record pediatric labeling information into a set of Oracle tables that are fully integrated with the Centerwide Oracle Management Information System (COMIS).

When installed on a PC with Windows 95, the form is accessible from the desktop by simply clicking on the pediatric labeling icon. The pediatric labeling data entry programs have been implemented in all of ORM's document rooms. They will be implemented in the Office of Generic Drugs in the next few weeks.

The next step is the development of an on-line query screen for CSOs, project managers and reviewers. A Pediatric Labeling Committee has been formed to help with development of the system. If you would like to join the committee or have input into development of the query screen and reports, please contact Helen Mitchell (MITCHELL) of OIT.

Sally Newman is a computer specialist in the Division of Applications Development and Services.

FDA Proposes Alcohol Warning for All OTC Pain Relievers

FDA announced in November that it intends to require an alcohol warning on all over-the-counter (OTC) pain relievers, which include aspirin, other salicylates, acetaminophen, ibuprofen, ketoprofen and naproxen sodium.

The proposal follows an extensive FDA review of data on the effect that consumption of alcoholic beverages can have on users of various OTC analgesics. The proposed warnings are designed to alert consumers about the specific risks that may be posed by the interaction of heavy alcohol consumption and the use of different types of OTC analgesics.

"Consumption of excessive alcohol while taking pain relievers can be dangerous to your health," said Lead Deputy FDA Commissioner, **Michael A. Friedman, M.D.**

The proposal includes the following warning statements:

- For acetaminophen-containing products—"Alcohol warning: If you drink three or more alcoholic beverages daily, you should ask your doctor whether you should take [product name] or other pain relievers. [Product name] may increase your risk of liver damage."
- For aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium and sodium salicylate-containing products—"Alcohol Warning: If you drink three or more alcoholic beverages daily, ask your doctor whether you should take [product name] or other pain relievers. [Product name] may increase your risk of stomach bleeding."
- For products containing combinations of the above analgesic categories—"Alcohol warning: If you drink three or more alcoholic beverages daily, ask your doctor whether you should take [product name] or other pain relievers. [Product name] may increase your risk of liver damage and stomach bleeding."

The issue of potentially harmful interactions between pain relievers and alcohol was the focus of a Nonprescription Drugs Advisory Committee meeting on June 29, 1993. At that meeting, the committee concluded that alcohol abusers or heavy drinkers are at increased risk for developing liver toxicity when using acetaminophen.

However, committee members were concerned that an alcohol warning on OTC drug products that contain acetaminophen in the absence of a similar warning on other pain reliever products would lead alcohol abusers to switch to products that contain other analgesic ingredients, which might pose equally significant, but different, risks.

On Sept. 8, 1993, the Nonprescription Drugs Advisory Committee met jointly with the Arthritis Drugs Advisory Committee to reconsider this issue and concluded that the use of aspirin, ibuprofen, or naproxen sodium increases the risk of upper gastrointestinal bleeding in heavy alcohol users or abusers and made a formal recommendation for FDA to require an alcohol warning on these OTC pain relievers. The FDA proposal would require a consistent warning

FDA has already required an alcohol warning for the new pain relievers previously marketed as prescription drugs and now available over-the-counter. These include naproxen sodium and ketoprofen.

Leadership Fellows Corner

Reflections on CDER's Transformation Challenges

By Joyce Korvick, M.D.

Over the past year, I had the good fortune to participate in the first CDER Leadership Fellows class. As I started, I really didn't have a good idea about what we were expected to get out of the program. As the year progressed, however, we were exposed to many interesting things:

- The CDER Change Team.
- "Benchmarking" with organizations who are trying new and successful approaches to their work.
- The National Performance Review.
- Current management styles used by private industry.

Change, change, change. Was it all just a dream, a fantasy, the latest fad? Could a government bureaucracy become innovative and proactive? Could we change? Or would we just keep on doing the same thing?

As the year concluded, I was still asking questions. I started looking more critically at the world around me. There were several pieces of information which convinced me that this new style of management was more than just a fad.

First I read the Blair House Papers. You can find them at http://www.npr.gov/library/papers/bkgrd/blair.html. This book contains the President and Vice President's reinvention marching orders to the Cabinet. It outlines the changes and innovations that can and should take place throughout the Executive Branch. It challenges all of us to find new solutions to old problems, to think "outside the box." It calls us to innovation and to new ways of doing business, which will bring about more efficient and responsive Federal agencies.

The second piece of information was the ongoing transformation effort in the British Government. Reading about their efforts convinced me that not only here, but abroad, new concepts were being employed in government.

Finally, review of the current business literature is full of examples which speak to the Information Age, the rapidly changing work environment and the need for efficiency. Innovation, is the key.

Where does that leave CDER? We have seen change in our organization. We have restructured and met the challenges of user fee goals. The Innovations in American Government Award (see September *Pike)* acknowledges our progress in facing change. However, many organizations meet the challenge of change by brut force. I have observed that many of our rapid approvals were accomplished, not because we were different, but because dedicated people were willing to work that much harder. Now we need to work smarter. What will that take?

We are now being called to transformation—a deeper and more profound change. Our external partners, who are also facing rapid changes, will not be willing to work with an antiquated government agency that is incapable of meeting their needs. How will we get to the CDER of the future? Yes, we have to align with our Mission, Vision and Operating Principles. We have to make them real. How do we do that? Dialogue, individual accountability and a leadership style among management which truly espouses these principles for all.

I recently attended a meeting where well-known business management consultant Peter Senge defined mission, vision, and operating principles. I will share this with you in the hope of making them more real to you.

Mission, simply put, is the reason or purpose for being. You never achieve your purpose. It is what your journey is about. Passion comes from purpose. Vision is the picture we seek to create in the future that we are trying to bring to reality (results). Operating principles are the values upon which we are all held accountable.

Why does a sense of mission or purpose matter? It instills passion and patience for the long journey. It serves as an anchor for results. Current business management strategies are exploring innovative ways of tapping into the intrinsic motivation of employees based on the idea that all people have a deep longing to make a difference. CDER is not in it to make a profit, but we are in it to make a real difference in peoples' lives. There lies the passion.

CDER of the future has many challenges and opportunities. In order to meet these, everyone in the organization needs to acquire new skills and begin to change his or her mental model of how things can be done. Management and leadership founded on principles which foster the growth, learning and creativity of individuals and teams are the basis for transformation.

All of us are challenged to understand those posters plastered on the walls. Have you ever sat down with others to talk about our Mission, Vision and Operating Principles? How can we make them real? How do they affect our everyday work? That is when the work of CDER's transformation begins—when we get out of our boxes and start talking.

Joyce Korvick is a medical officer in the Division of Special Pathogens and Immunologic Drug Products

Communications Corner

Secrets of Great Speakers

Successful speakers share certain practices and techniques. They make it a point to entertain as well as inform. They also deepen and expand the bond with their audiences through openness, sensitivity and humor. Good speakers:

- Are thoroughly prepared and comfortable with their material.
- Outline their main points on a slide, easel or blackboard.
- Involve their audiences by soliciting answers and information.
- Enhance their presentations by creative use of newspaper clippings, cartoons, music, appropriate quotes or relevant experiences.
- Often use self-deprecating humor to get a point across.
- Move around the room.
- Avoid boring audiences with material that's common knowledge.

Source: Carol Driscoll writing in *The Toastmaster*, P.O. box 13888, Mission Viejo, CA 92690 in *communications briefings*, 12(3).

Satellite Video Updates Industry on Adverse Event Reporting

(Continued from page 1)

adverse event reports, and the Center monitors and analyzes the reports. Under AERS, industry data will arrive electronically in an International Conference on Harmonization format and precoded according to an international nomenclature.

The first panel discussed the new guidances and regulations concerning adverse event reporting, as well as related compliance considerations. Panel members were **David Barash,** who is responsible for overseeing the identification of signals of serious and unexpected reactions for the Office of Epidemiology and Biostatistics (OEB); **Nancy Haggard,** postmarketing adverse drug experience program manager in the Office of Compliance; Deputy Center Director (Review Management) **Murray Lumpkin, M.D.;** and **Audrey Thomas,** from the Regulatory Policy Staff, who is responsible for revising the adverse drug reaction regulations to comply with International Conference on Harmonization (ICH) initiatives.

If you are on the Internet, click here to view photographs.

The second panel provided an overview of the information technology systems that will provide stronger data management and data analysis tools. Panel members were **William Calvert,** who oversees an information technology program in OEB that provides data and computing technology services to support Pharmacovigilance activities; **Dr. Lumpkin; Robert Nelson, Ph.D.,** who, as associate OEB director for epidemiology, spearheads the Center's efforts at re-engineering the postmarketing surveillance program; and OEB Director **Robert O'Neill, Ph.D.**

Answering the telephones and fax machines were experts who were able to help callers phrase their questions succinctly and funnel those with the most general interest to the panels. They were **Mia Chen, Thomas Kuchenberg, Ralph Lillie, Denis Mackey, Toni Piazza-Hepp,** and **Fred Richman,** all from CDER, and **Dianne Kennedy** from the Office of the Commissioner**.**

The program was produced by OTCOM's **Elaine Frost.** CDRH staff included **Glenn Scimonelli,** director; **Bob Futula,** assistant director; **Bruce Butler,** on-line editor; and a large postproduction staff.

In addition to providing co-sponsorship, FDLI coordinated publicity, downlink sites and follow-up evaluations. "Videoconferencing reaches a lot more people and is more convenient for our members," said FDLI satellite videoconferencing coordinator Tracy Campos. "They can watch at their own company if they have the satellite downlink equipment. We also provide audio only access. FDLI acquires the audience, and FDA provides the production and content."

Tapes of the show are available for a fee from FDLI at (202) 371-1420. FDA staff may borrow copies from OTCOM's Medical Library (Parklawn 11B-40) or Division of Training and Development's Learning Resource Center (Parklawn 12B30).

Patient Testing, Labeling Strengthened for Diabetes Drug

The FDA announced on Dec. 1 that patients taking the diabetes drug troglitazone (Rezulin) should be monitored more frequently for signs of injury to the liver. In addition, warning information about potential liver toxicity will be more prominently featured in the drug's labeling. These actions, taken with the full cooperation of the drug's manufacturer, re-emphasize for health care providers and patients the importance of monitoring patients taking troglitazone to ensure that it is used in the safest manner.

Troglitazone is used in combination with insulin or sulfonylurea in patients with Type 2 diabetes (adult-onset diabetes mellitus) whose blood glucose levels are not adequately controlled by these other therapies alone.

On Nov. 3, FDA and the drug's manufacturer announced changes in the prescribing information for troglitazone, including a new warning and recommendations for monitoring liver function. In making these changes, FDA was aware of approximately 35 postmarketing reports of liver injury among U.S. and Japanese patients taking troglitazone, including liver failure leading to one liver transplant and one death.

At that time, FDA asked for reports on additional adverse events associated with the use of troglitazone, and the Agency has now received a total of approximately 150 adverse event reports, including three deaths from liver failure linked to the use of troglitazone in Japan. Approximately 600,000 patients in the United States. and 200,000 in Japan have been treated with this drug. The deaths in Japan occurred in patients treated before a stronger label warning and recommendation for liver enzyme testing took effect there.

FDA has concluded that liver enzyme levels should be measured in patients taking troglitazone at the start of therapy, every month for the first six months of treatment, every other month for the next six months and periodically thereafter. In addition, liver function tests should be performed on any patient on troglitazone who develops symptoms of liver dysfunction, such as nausea, vomiting, fatigue, loss of appetite, or dark urine and jaundice. The product's current labeling advises that patients with significant elevation of these liver enzymes stop taking the drug. Previously, liver enzyme testing was recommended during the first two months of therapy and then every three months.

The increased monitoring of patients taking troglitazone is designed to detect those few patients in whom use of the drug can lead to serious liver damage. The manufacturer of the drug has sent a letter to U.S. health care professionals to inform them of these changes. Although, FDA will carefully monitor and evaluate reports of liver problems associated with troglitazone. At present the Agency continues to find the benefits of troglitazone outweigh the risks for treating appropriately selected and monitored diabetes patients.

PQRI Corner

Center, Industry, Academia Collaboration Targets Research

By Karl Flora and Ajaz Hussain

In February, the first public meeting of the Product Quality Research Initiative (PQRI) will formally debut this novel approach to discovering ways to achieve regulatory relief for the pharmaceutical industry. Modeled on the research-to-policy-to-review paradigm of the Office of Pharmaceutical Science, PQRI is an attempt to build a consortium among academia, the pharmaceutical industry and the Center. The aim is to develop, through comprehensive research and collaboration, a strong scientific basis for regulatory guidance development and regulatory decisions to ensure high standards of drug product quality and performance.

The initiative has parallels to the highly successful Scale Up and Post Approval Changes (SUPAC) guidance. The pharmaceutical community has viewed SUPAC as a "paradigm shift" in the right direction. Cost savings have been projected by a panel of scientific leaders to be on the order of hundreds of millions of dollars a year. An FDA contractor conservatively estimated the savings to industry at $50 million a year. The estimated cost of the research portion of SUPAC was about $5 million over a three-year period. For every Federal dollar spent on this research, the U.S. economy has saved $10.

During a period of intense constraint on the Federal budget, however, the use of Agency funds for this type of research on the scale needed is virtually precluded. With the growth of the pharmaceutical industry and the successful introduction of hundreds of new drugs in the last several years, the need for regulatory relief grows ever more imperative.

PQRI steps into the breach with a process for industry, academia and the Center to collaborate on focused research and policy development projects designed to meet the challenges associated with the product quality aspects of drug development and evaluation. The proposal is being developed in cooperation with several trade associations. The specific and targeted research proposals identified through the PQRI process should be self-evidently worthy of funding to the pharmaceutical industry. Research could be performed in academia, in the FDA's own labs or by the pharmaceutical industry itself. Results would be reviewed by the Center before being incorporated into new guidances.

The proposed structure of PQRI consists of a steering committee, a resources committee, a series of five technical committees, and an education, training and assessment committee. Membership in the committees is divided evenly among representatives from the Center, academia and industry. The steering committee identifies, prioritizes and monitors appropriate PQRI outcome measures. The five technical committees focus on drug substance, drug product, biopharmaceutics, science management and novel approaches. Each technical committee will define applied research topics, establish priorities, evaluate research proposals, select working group members to focus on specific projects, implement research objectives and evaluate the regulatory impact of research programs.

The interface between the Center and the PQRI is through the appropriate Center policy coordinating committees, primarily Biopharmaceutics and Chemistry, Manufacturing and Controls. Already, an ambitious research agenda has been identified for the technical committees. The next steps include:

- Defining demonstration projects.
- Identifying working groups and members.
- Establishing a cooperative research and development agreement (CRADA) between the FDA and the American Association of Pharmaceutical Scientists (AAPS) as the basis for a neutral environment for PQRI activities.
- Holding the public workshop.
- Completing demonstration projects.
- Evolving the PQRI into an independent foundation—the PQR Institute.

The purpose of the February public meeting is to introduce PQRI to industry and academia, present results from FDA-sponsored research and provide input to the steering and technical committees. Details on registering for the February meeting can be obtained from the host organization, University Pharmaceuticals of Maryland, Inc., at the following Web site: http://www.upm-inc.com.

Karl Flora, Ph.D., and Ajaz Hussain, Ph.D., are the director and deputy director, respectively, of the Division of Product Quality Research.

New ODE IV Director Picked

M. Dianne Murphy, M.D., currently professor of pediatrics and chief of the General Pediatrics Division at the University of Florida Health Science Center at Jacksonville, has been named the new director of the Office of Drug Evaluation IV. Dr. Murphy's start date will be March 1. Until then, **Murray Lumpkin, M.D.,** Deputy Center Director (Review Management) will continue as acting ODE IV director.

Originally from Virginia, Dr. Murphy attended Virginia Polytechnic Institute and received her M.D. degree from the Medical College of Virginia. After completing a pediatric residency at the University of Virginia, she did her fellowship in pediatric infectious diseases at the University of Colorado. Following her fellowship, she was an assistant professor of pediatrics at the University of Texas Health Science Center at San Antonio, followed by a seven-year stint as associate professor of pediatrics and medical consultant to the diagnostic virology laboratory at the University of Tennessee Medical Center at Knoxville. She has approximately 30 articles in peer-reviewed publications.

From 1990 to 1993, Dr. Murphy was the assistant director for medical affairs in the Division of Anti-Viral Drug Products. In 1993, she left CDER for her current position.

First Responders Enhance Safety in Their Communities

(Continued from page 1)

broken. She insisted that the driver not get out of the car and sit quietly until the rescue squad arrived. When help appeared in the form of an off-duty fireman who knew the driver, Kathy handed off care. She later learned that the driver had a history of back and neck problems and was taken to a hospital on a backboard. By encouraging the driver to stay put until help arrived, Kathy may have helped prevent additional trauma.

Barely three weeks after graduating and on his way home from work, Gregg came upon a two-car accident involving a small car and a larger one. The passengers in the small car were a man and his teen-age daughter. The passengers in the larger sedan were a woman and her 4-year-old son. When Gregg arrived, the three older persons were on the ground amid broken glass. The initial bystanders had apparently misinterpreted the light-colored dust that arose from the airbags as smoke and had removed the victims from their cars.

Gregg immediately identified himself as a First Responder, sent the bystanders to call 911 and quickly triaged the victims as he had been taught. He determined that everyone was conscious and no one had immediate life-threatening injuries, although the man was having chest pains. The small boy had been in a protective seat and was uninjured.

When Gregg went back to assess the victims in more depth, he discovered that the teen-ager had serious injuries to her hips and legs. He covered her with a blanket to treat for shock and reassured her that help was on the way. Her father reported no previous history of heart problems, and Gregg thought it likely that he had struck the steering wheel. Using a cellular phone, Gregg reported his assessment to the 911 dispatcher who relayed the information to the in-coming rescue squad.

Two rescue squads quickly arrived from Station 8 in Gaithersburg. Several emergency medical technicians (EMTs) attended to the teen-ager. Gregg assisted another EMT who examined her father. The Medi-Evac helicopter was called for the teen, and the other victims were transported to the hospital.

The Gaithersburg Rescue Squad praised Gregg's efforts, and the squad captain expressed appreciation for Gregg's willingness to assist the EMTs who arrived on the scene. The rescue squad emphasized that removing accident victims from their cars may cause additional serious injuries.

Angel Clark Burba, a paramedic and the instructor for the First Responder course, was "really proud of her students." She described the training as "a means to teach the lay public some aspects of emergency medical care so they do not exacerbate injuries while keeping themselves safe at an accident scene."

She said that students develop a knowledge of what emergency medical care is about and what its limits are. Angel stressed that a First Responder would have known not to remove victims from their vehicles because of the risks involved. "The one thing I hope everyone takes away from this training is thinking," she said. "Clearly, Kathy and Gregg have done that. It's important to know that it isn't necessary to act impulsively to do the safe thing. In every case, taking time to think is the first thing to do."

Pam Fagelson is a management analyst in the Division of Planning Evaluation and Resource Management.

Safety Committee Spearheaded Emergency Training

By Pam Fagelson and Carol Norwood

CDER's Occupational Health and Safety Committee has recently sponsored a First Responder course as part of its continuing Centerwide safety program. Since CDER offices located outside the Parklawn Building lack a health unit that can provide first aid, the committee initially targeted employees in these buildings for First Responder training.

The goal is to have at least two staff members at each site trained and equipped to deal with emergencies until the rescue squad can arrive. Response to the first class was excellent, and there are now 22 trained employees located at the Center's sites in Rockville and Gaithersburg. First aid and CPR kits have been received for the responders in each building.

The Occupational Health and Safety Committee was formed in 1996 to develop, promote and assist the safety officer in implementing a Centerwide safety program focused on providing a safe work environment for all employees. The committee takes particular interest in emergency response, ergonomics and indoor air quality. It has representatives in each building to help identify problems. The committee meetings rotate to the various sites so members become more familiar with the facilities and local issues.

A Web site is planned that will have a variety of safety information. While not a substitute for having emergency numbers close at hand, the Web site will be an easy reference for emergency contacts, committee members, phone numbers, evacuation plans and information on workplace health and safety topics.

The graduates of the initial First Responder course are: **Kathy Abel, Patricia Alcock, Mark Askine, Brenda Atkins, Shukal Bale, Donald Carrington, Christina Chi, Gregg Davis, Pam Fagelson, Jean Grimes, Wanda Logan, Connie Norris, LuAnn Pallas, Susan Papermaster, Lynnda Reid, Vibhakar Shah, Toy-Ping Taira, Craig Thomas, Rajendra Uppoor, Marilyn Welschenbach, Tonya Wise** and **Ita Yeun.**

The CDER safety officer is **Edward Radden,** Office of Management, (RADDENE). The acting committee chair is **Linda McGee,** Office of Compliance, (MCGEE).

Pam Fagelson is a management analyst in the Division of Planning Evaluation and Resource Management, and Carol Norwood is a management analyst in the Executive Operations Staff.

Lucy Rose Leaves OTCOM Strong, Well-Managed

By Janet Woodcock, M.D.

Office of Training and Communications Director **Lucy Rose** will be leaving CDER at the end of December to take on new challenges as a private consultant. **Linda Brophy** will serve as acting director. Lucy joined the government and began her work in CDER as a reviewer in the Division of Drug Marketing, Advertising and Communications. As division director, she managed that division during some of the tumultuous times when former Commissioner Kessler was deeply involved in strengthening the Agency's role in regulating advertising.

Several years ago, at my request, Lucy left the world of pharmaceutical advertising and became the director of the newly formed OTCOM, an entity she had suggested. Her job involved pulling together the disparate Center components involved in training and communication activities and merging them into a strong, unified group. Lucy and her team in OTCOM have succeeded in this beyond anyone's wildest expectations.

CDER's internal and external communications have improved dramatically. Our *News Along the Pike,* our Web page, our satellite videoconferences and numerous other activities are truly models of effective modern communication. Our newly renovated Medical Library is a pleasure to use.

The Center's training activities are becoming aligned with our performance expectations. The CDER orientation, and the New Reviewer's Training are well received and effective. OTCOM's writers and editors were responsible for our successful application to the Innovations in Government Award, and our win was facilitated by their excellent write-up.

In addition, Lucy has been deeply involved in the CDER transformation efforts, our Leadership Fellows Program and many other important Center activities.

I know I speak for the whole Senior Management Team in thanking Lucy for her commitment to our work over the last three years. Lucy has brought energy, passion and a results orientation to our efforts. She has always pushed for clarity and resolution of difficult issues, and she has been an important member of our team.

She leaves a legacy of a strong, well-managed office with outstandingly successful programs.

Janet Woodcock is the Center Director.

FDA Proposes Expanding Clinical Hold Regulations

In September, the FDA proposed a rule that would allow the use of the clinical hold to prevent the exclusion of women of childbearing potential from all phases of clinical trials for drugs to treat life-threatening illnesses. The proposed rule would apply only to studies involving life-threatening illnesses. It would not impose enrollment or recruitment requirements. The proposed rule is written from a gender neutral perspective, but is intended to ensure that women with a life-threatening illness are not excluded solely because of their reproductive potential. The clinical hold would be used only if other efforts to eliminate the exclusion had failed.

Current regulations allow the use of a clinical hold primarily for safety reasons, particularly in Phase I. In addition to safety concerns, a later phase study may be placed on clinical hold if the study is not adequate and well-controlled.

This proposal reflects a significant evolution of thought during the past two decades about the participation of women of reproductive potential in clinical studies and is in keeping with the agency's 1993 *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*. The 1993 guideline encouraged women's participation in all phases of clinical trials and revoked a 1977 recommendation to restrict the participation of women with reproductive potential, especially in early trials.

The earlier recommendation to restrict participation reflected the protective environment with regard to women brought about by the thalidomide experience a decade earlier. Although the 1977 recommendation explicitly did not apply to trials to treat life-threatening illnesses, women were largely excluded from such trials. The 1993 guideline advised leaving the decision about the participation of women with reproductive potential in all clinical trials to patients, investigators, sponsors and institutional review boards.

Recent but limited Agency surveys of some applications have revealed that women are still being excluded because of their reproductive potential from some clinical trials involving drugs for life-threatening illnesses. These findings were substantiated by testimony from patients and representatives of patient advocacy groups who participated in meetings and public workshops in 1994 and 1995.

The change being proposed in the clinical hold regulations is based on several factors, including recommendations from the National Task Force on AIDS Drug Development and the Presidential Advisory Council on HIV/AIDS. After lengthy discussions with industry and the public, the Agency focused on four key factors in developing the proposed rule:

- The Agency is committed to expanding patient access to new therapies for life-threatening diseases and accelerating the approval of these drugs.
- Important ethical principles underlie the belief that no volunteers should be excluded from any phase of a clinical trial involving a life-threatening disease solely because of their reproductive capability. Potential participants should be thoroughly informed of any real or potential risks and decide for themselves whether or not to take part.
- Mechanisms are available to protect individuals who participate in clinical trials from potential risks.
- The Agency is committed to expanding the collection of gender-specific data on investigational therapies.

The clinical hold would only be used as a last resort when all attempts to resolve the matter with the sponsor had failed. Comments on the proposed rule are due by Dec. 23.

FDA Changes to Have Big Short-Term Impact on CDER

(Continued from page 1)

Of critical importance to CDER is the reauthorization of the Prescription Drug User Fee Act (PDUFA). The Modernization Act extends PDUFA for five more years, through fiscal year 2002. The act contains changes in how fees are assessed and collected. For example, fees are waived for first applications for small businesses, orphan products and pediatric supplements.

In addition to renewing PDUFA, the Modernization Act contains a number of provisions that will change the way the Agency works and the way the centers perform product reviews. Some provisions will make the process easier. But others will increase staff workload, especially over the short term, as new regulations and guidance documents are developed.

"The bill creates heightened expectations for Center responsiveness in some areas . . ."

The act creates heightened expectations for Center responsiveness in some areas, for example, in overseeing "fast-track" drugs and in developing regulations and guidances for industry under new provisions for disseminating information on off-label uses.

The following is just a peek at some of the more interesting provisions of the act.

- The act codifies FDA's accelerated approval regulations for "fast-track" drugs and requires guidance on fast-track policies and procedures within one year. A fast track drug is one that demonstrates the potential to address unmet medical needs and is intended to treat a serious or life-threatening condition.
- The National Institutes of Health, in consultation with FDA, will maintain a database of information on clinical trials for serious and life-threatening diseases. The database will include eligibility criteria, location of sites and points of contact for enrollment.
- An extra six months of exclusivity will go to sponsors who complete requested pediatric studies within an established time frame.
- Sponsors can distribute reprints of articles from peer-reviewed journals after they meet a number of conditions. The information is subject to balance requirements and corrective actions if FDA finds them necessary.
- Health care economic information can be provided to formulary committees, managed care organizations and similar entities with drug selection responsibilities if it is based on competent and reliable scientific evidence.
- The agency must issue guidance for NDA reviewers. Guidance should address a number of issues, including promptness in conducting the review, technical excellence, lack of bias, conflict of interest and knowledge of regulatory and scientific standards. Also included are parameters for meeting with an NDA applicant to attempt to agree on the design and size of clinical trials intended to form the primary basis of an effectiveness claim. Any agreed-upon clinical trial parameters should be included in the administrative record and no changes can be made in the parameters unless specified events occur. There are parallel requirements for IND applications and abbreviated applications for generic drugs.
- The section of the act related to insulin products has been repealed because it was obsolete.
- The section of the act that dealt with the approval of antibiotics has been repealed and specific procedures for handling antibiotics are included.
- The act codifies the reinventing government initiatives that are part of the Scale-Up and Post-Approval Changes (SUPAC) guidances. It distinguishes between major and minor manufacturing changes and establishes a 30-day notification period for certain supplements.
- The act provides a framework for FDA to write regulations that distinguish acceptable pharmacy compounding from the unacceptable manufacturing of unapproved new drugs. It places controls on bulk drugs used for compounding, the amounts of compounded drugs that are essentially copies of commercially available drug products and compounded drugs shipped across state lines.
- Finally, the Agency must review good guidance practices and issue regulations by July 1, 2000.

PDUFA performance goals agreed to by the Agency and industry are outlined by HHS Secretary Donna Shalala in a Nov. 12 letter to members of Congress. The letter and goals are be available on the CDER Web site by selecting the Regulatory Guidances button, and the goals are available directly at:

http://www.fda.gov/cder/news/pdfufagoals.htm.

A full text copy of the Modernization Act is also available by choosing the What's Happening button or directly at:

http://www.fda.gov/cder/guidance/s830enr.txt.

Nancy Derr is a policy analyst in the Regulatory Policy Staff.

New Review Division Director Named

Gary K. Chikami, M.D., has been named the new director for the Division of Anti-Infective Drug Products in the Office of Drug Evaluation IV. He will continue as acting director until his official start date of Dec 21. Originally from California, Dr. Chikami attended Pomona College where he received a B.A. in psychology prior to receiving his M.D. degree from the University of California, San Diego. Dr. Chikami is board certified in both internal medicine and infectious diseases.

From 1987 to 1990, Dr. Chikami was assistant professor of medicine in the division of infectious diseases at the UCLA School of Medicine. In 1991, he joined FDA as a medical reviewer in the division of anti-viral drug products and became the acting deputy director of that division in October 1996. In May, 1997, Dr. Chikami was named acting director of the Anti-Infective Division.