news along the pike

DECEMBER 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

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INSIDE . . .

CDER'S CORNERS

Risk Management Workshop: "Seminal Event"

Maximizing Public Health Benefit Seen as Overarching Goal

A risk management workshop attended by more than 250 CDER reviewers on Nov. 15 and 16 was hailed as a "seminal event" by Center Director **Janet Woodcock, M.D.** The workshop signals a new focus for the Center and marks a willingness to maximize the public health impact of its work, she said.

The timing of the workshop was "exquisite," she said. "A broad coalition of people within and outside government are concerned with the issue," she said, "and we can push our vision for patient safety and public health forward."

The workshop, organized by OTCOM's Division of Training and Development, was designed to provide a basic understanding of risk management and the science and theory behind it. It provided reviewers with a common language and a general context for the issues in both the health care setting and the regulatory environment.

The format for the workshop included formal presentations from outside experts and internal CDER speakers, followed by small group discussions on how to apply risk management concepts to the CDER environment and improve risk communications with stakeholders.

Videotapes of the workshop will be available to all CDER offices in mid-January. Speaker biographies and handouts are available on the Center's intranet at http://cdernet.cder.fda.gov/dtd/handouts/fall99/riskmgmt/rm.htm. Clicking on the names highlighted in blue below will also access the handouts.

In her welcoming remarks, Dr. Woodcock

(Continued on page 6)

FDA Launches Internet Pharmacy Information Website

Consumers Can E-Mail Complaints About Illegal Activities

FDA announced on Dec. 20 that it has established a new Internet Website to provide consumers with useful, easy-to-understand information about buying prescription drugs and medical products online. This public outreach initiative is part of FDA's action plan to increase public awareness about the health, economic and legal risks of online sales of prescription drugs and medical products.

Increasingly, consumers are using the Internet to purchase medical products. Due to the ease with which a Website can be created, a site may appear to be a legitimate pharmacy when in fact both the seller and the product sold are illegitimate. Consumers need to know the risks—and how they can protect themselves—when buying prescription drugs and medical products on the Internet.

"The development of the Internet has opened up many new options for consumers to purchase products more conveniently," said FDA Commissioner **Jane Henney, M.D.** "However, the Internet has also provided unscrupulous individuals with immense new opportunities to promote and sell prescription drugs unlawfully to unsuspecting patients."

By visiting FDA's homepage at http://www.fda.gov and clicking on the banner, Buying Medical Products Online, consumers can access the new site. The Website contains information on how consumers can:

- Obtain information on how to protect themselves from dangerous online practices involving the sale of FDA-regulated products.
- Learn about FDA's enforcement efforts.
- Find out how to spot health fraud.
- Get a list of answers to the most commonly asked questions about Internet drug sales.

Instructions on how to notify FDA are included for consumers who suspect that a Website is illegally selling human or animal drugs, medical devices, biological products, foods, dietary supplements or cosmetics over the Web.

An electronic e-mail form is provided for most complaints. Instructions on how to telephone FDA in life-threatening situations or report serious reactions through MedWatch are also included.

JOE'S NOTEBOOK

Greetings to Pike's Contributors

While you're enjoying the holiday mood, stop and take time to thank your friends and colleagues who contributed to the Pike last year. Each took time from a busy schedule and pressing duties to share something important with you, and they are:

Tanya Abbott, Richard Allen, Laura Alvey, Carol Assouad, Jackie Barber, Margaret Bell, Celeste Bové, Greg Brolund, Bronwyn Collier, Jerry Collins, John Emelio, Emmanuel Fadiran, Pam Fagelson, Mike Fossler, Elaine Frost, Rita Hassell, Shelley Johnson, Debbie Kallgren, Iris Khalaf, Lydia Velazquez Kieffer, Ken Kobayashi, Thomas Layloff, Pat Leonard, Larry Lesko, Murray Lumpkin, Tim Mahoney, Amy Mason, Melissa Maust, Judy McIntyre, Debbie McKemey, Kate Meaker, Justina Molzon, Jack Morin, Jim Morrison, Janice Newcomb, Chris Nguyen, Lydia Papio, Kathy Robie-Suh, C. Russ Rutledge, Vanitha Sekar, Ted Sherwood, Robert Shore, Tony Sims, Milton Sloan, Diane Smith, Gloria Marquez Sundaresan, Donna Volpe, Grant Williams, Roger Williams, Pam Winbourne, Janet Woodcock, Robert Young and **Scott Zeiss.**

World AIDS Day, Dec. 1, passed without much fanfare at the Center. However, HHS Secretary **Donna Shalala** noted that it's appropriate to reflect on the sorrow that this deadly disease has brought and also to look forward with hope to the promises that lie ahead in the new millennium.

"We know all too well the tragedy of this disease—more than 688,000 Americans have been diagnosed with AIDS and more than 410,800 have lost their lives since the epidemic began in 1981," she said. "Worldwide, the toll is even more devastating with an estimated 2.6 million deaths and 5.6 million new HIV infections this year alone, according to a recent report by the United Nations AIDS program."

There are encouraging developments. From 1995 to 1998, AIDS related mortality in the United States dropped from 50,000 deaths a year to an annual rate of just under 20,000. Since 1987, AIDS has fallen from the No.1 killer overall to the 16th. There are more HIV/AIDS therapies than ever before. More people are in care and receiving these vital drugs, living longer lives in better health. Investment in AIDS research has grown greatly. New investments to develop a vaccine are well underway.

The secretary noted that the time for approving new AIDS drugs is shorter than ever before and that more new drugs are in development. "We have more access to rural care, more primary care and more treatment than ever before," she said.

"In spite of the progress, we must also recognize that we are a long way from winning this battle. Although overall AIDS mortality rate is beginning to stabilize in this country, AIDS death rates in the U.S. remain nearly 10 times higher among African Americans than whites," Shalala said. "If we are to continue to make progress in eliminating health disparities in the next century, a key to our efforts will be prevention, particularly in communities of color."

She warned against becoming complacent about the nation's progress and called for strengthening and expanding prevention programs.

"Finally, it is fitting this World AIDS Day is focused on the world's children—particularly those who have been orphaned by AIDS. Fortunately, a major success has been achieved in preventing new HIV infection among babies, with a 73 percent decrease in new AIDS cases among infants. Our greatest treasures and our greatest hope for the future are our children. It is for them that we must never give up the fight to end this terrible disease."

news along the pike

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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).

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

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OMBUDSMAN'S CORNER

CDER's Pet Peeves—Part 1

As part of our transformation to a more transparent organization, we have provided many opportunities for the industry to air complaints about CDER. During a recent meeting with industry folks, the suggestion was made that I let them know what most bugs the Center's staff about the industry. I conducted an informal, Centerwide e-mail poll, and I'm using this column and the next to report the results.

I received a wide spectrum of responses. Some expressed appreciation for the opportunity and then unloaded lists of grievances. At the other end of the spectrum were comments that the industry pretty much has its act together. I have grouped the complaints into four main categories: interactions, operational and submission quality, expectations and gaming the system.

Overly Aggressive Interactions

By far the most common complaints involved what are perceived as overly aggressive contacts by industry representatives. This type of behavior includes:

- Calling very frequently regarding the status of a document or review.
- Repeatedly asking the same question looking for the desired answer (either asking the same person the question in different forms or shopping around in different offices for the desired answer).
- Leaving a message for someone and then calling his or her supervisor shortly thereafter complaining that calls are not being returned.
- Failing to control anger, using inappropriate and demeaning statements to staff (almost always when a manager is absent).
- Insisting on an estimate of completion dates of reviews before anyone has looked at the submission.
- Asking for early warning of possible problems and then demanding a meeting with the division to discuss the problems before they have had supervisory review.
- Bypassing several levels in the supervisory chain to bring problems to senior management that could be solved at a lower level.

In general, I believe most CDER staff understand the time pressures industry people face and are sympathetic to their sense of urgency about products. These complaints stem from behavior that goes beyond normal angst.

I always recommend to applicants that they determine with the CDER project manager for their application what is reasonable in the way of status checks. In anyone's book, the several status calls a day that some complaints cited are excessive.

Most of the complaints are self-explanatory. However, the difference between early warning about bad news and premature alarm deserves more discussion.

"I always recommend to applicants that they determine with the CDER project manager for their application what is reasonable in the way of status checks."

Clearly, industry scientists want to learn of potential problems as soon as possible. But do applicants really want to know what concerns reviewers at every step? Besides generating ulcers, what is an applicant going to do with such information?

Unless everyone at CDER who needs to evaluate the potential problem has done so, the applicant runs the risk of getting an incomplete picture of the problem or perhaps doing unnecessary work. On the other hand, if concerns can be allayed by pointing out information in the submission, early, informal contact may save substantial time.

My recommendation is that applicants wait for at least a supervisory review before pushing for insights on potential problems and that such issues be broached by reviewers in the form of neutral questions to minimize alarm.

Other complaints about interactions focused on administrative or protocol problems, such as:

- Contacting a reviewer directly without going through the project manager.
- Bringing legal representatives and arguing legal issues at scientific meetings.
- Amending the agenda for a scheduled meeting at the last minute and sending in more data.

Operational, Submission Quality

Complaints about the quality of submissions and science ranked just behind aggressive interactions. They include:

- Submitting poorly organized or sloppy documents, for example: too much redundancy; poor pagination; unnecessary data—such as printouts from lab equipment; inconsistent data; and repeated mistakes.
- Ignoring advice on protocols and other input from previous meetings and correspondence.
- Not stating in a cover letter what is in the attached submission.
- Mixing important data in with routine submissions.
- Not identifying when data have been previously submitted.
- Submitting MedWatch forms with missing data and no assessment or explanation.

The quality of submissions and data sent to CDER varies widely. Overall, the quality of submissions has been improving steadily. Attention to detail, especially in aspects that make submissions more understandable, is well worth the time entailed.

Also, I would recommend that if an applicant does not want to follow the Center's advice on a protocol or suggestions provided in letters conveying deficiencies, it is wise to state that up front and to explain the reasons or, better yet, discuss plans with CDER. There may have been miscommunication about what is expected and the reasons for the advice or suggestions.

Early in the new millennium, I'll give you the rest of my survey results. Until then, have a great holiday season.

Jim Morrison is the Center's Ombudsman.

Electronic Regulatory Submission and Review Training Available

Do you have an electronic review coming soon, but aren't familiar with the software? How do DFS, PDF and all the other high-tech acronyms fit together?

You can find all of the information you need and more by attending one of the ERSR training courses offered monthly:

- *NEST:* Explore electronic NDAs in the NDA Electronic Submissions Training.
- *NEDAT* and *JMP:* Find out how to access, analyze and convert NDA data to various software applications in the NDA Electronic Data Analysis Training and the course on the JMP statistical software package.
- *Creating PDF Review Documents:* Once you've pulled the information you need from the electronic submission, attend this course to find out how to convert your review from Word or any other software to Portable Document Format.
- *DFS:* Checking your documents into the electronic repository is easy once you've attended the Division Files System class.

So sign up now for free OIT training. The winter 2000 training schedule is available on the OIT intranet (http://oitweb/) in the training section. You can also read class descriptions, obtain copies of all classroom documentation and register for any of the free computer classes offered by OIT.

The OIT Point of contact for ERSR training is **Tim Mahoney** (MAHONEYT). **Lana Kostecka** (KOSTECKAL) is the OIT training coordinator.

January IT Training

Monday	Tuesday	Wednesday	Thursday	Friday
3	**4**	**5**	**6**	**7**
10 **Excel** 1-4	**11** **CDER's Standard Letters System** 9-12 **JMP Session 1** 1-4	**12** **NEST** 9-12 **DFS** 1-4	**13** **Word Intro** 9-12 **Word Formatting** 1-4	**14** **Word Tables** 1-4
17	**18** **JMP Session 2** 1-4	**19**	**20** **DFS** 9-12 **NEDAT** 1-4	**21** **Creating PDF Documents** 9-12 **MS Project for CDER PMs** 1-4
24	**25** **JMP Session 3** 1-4	**26** **CDER's Standard Letters System** 9-12	**27**	**28**
31				

The catalog, training materials, schedule and online registration can be found at http://oitweb/.

Help Desk FAQ

Each month, OIT will feature a frequently asked question from the OIT Help Desk.

Q: How do I setup a network printer?

A: Follow these steps:

- Double click on the My Computer desktop icon.
- Double click on the Printers icon.
- Double click on the Add Printer icon.
- On the Add Printer Wizard screen, click Next button.
- Choose Network, then click Next button.
- Fill in the printer's network path name, which will look like \\CDFDA\PRINTER, where "PRINTER" is the eight-character name of the printer. Choose Yes for printing from DOS-based programs. Click Next button.
- Ignore the Capture Printer Port button. Click Next button.
- Choose manufacturer and type of printer. Click Next button.
- Fill in name of printer. Click Next button.
- Answer Yes if you want your Windows-based programs to use the printer as the default or No if you are installing an additional printer. Click Finish button.

For all IT support, contact the Help Desk (HELP, 7-0911).

QA Development Project Update

Project efforts are currently focused on developing project plan templates applicable to diverse OIT projects. Meetings are scheduled through December to collect sample planning materials and specific requirements from each OIT division. The templates will be included in an OIT guidance document on project planning. Information about this project is located on the CDER Intranet (http://oitweb/) under the OIT Activities button. The OIT point of contact is **Jerry Yokoyama** (YOKOYAMAJ).

PM Coordination Update

OIT senior managers as of Dec. 3 had approved nine baseline project descriptions. Approved project descriptions are screened for confidential and proprietary information and posted on the CDER intranet (http://oitweb/) under PM Coordination. Twelve additional projects have been reviewed. Of these, four were removed from the project list, five are being revised for approval, and three are being revised for a second review. A status summary of project reviews is available on the CDER intranet. A new project for wider distribution of the CDER Standard Letters system was reviewed; however, this project may be downgraded to an immediate implementation if CDER users find network-based operation acceptable.

The project management coordinator holds a status review with each approved project on a monthly basis. Six monthly status reviews have been performed. At each status review, the project manager is required to present information regarding completed and anticipated tasks, anticipated vs. actual resource expenditures, project risks and any issues needing elevation to a higher management level.

The OIT point of contact is **Vali Tschirgi** (TSCHIRGIV).

EEO CORNER

Center to Take Part in Martin Luther King Observances

BY GLORIA MARQUEZ SUNDARESAN

Starting four days after the Rev. Dr. Martin Luther King Jr. was gunned down by an assassin's bullet on April 4, 1968, African-Americans began a persistent, nationwide effort to seek a day of remembrance for the civil rights leader.

In November 1983, President Reagan signed legislation making the third Monday in January a federal holiday honoring King's birthday. King, a leader of the civil rights movement in the 1960s, embraced the Mahatma Gandhi's teachings of nonviolence in his struggle for civil rights.

King's "I Have a Dream" speech has come down as one of his most popular speeches. In that speech, he said he dreamed that someday in the future all children would be judged "not by the color of their skin, but the content of their character." King remains a revered leader for the civil rights of all people. For his non-violent struggles, he received the Nobel Peace Prize in 1964.

In the Center, we celebrate the holiday with activities, exhibits and programs to honor the man who gave so much of himself for the civil rights movement.

CDER is a member of the HHS Martin Luther King Commemorative Committee. The committee plans to hold a program in Parklawn with distinguished speakers, songs and music.

In addition, the committee sponsors a scholarship drive for the support of students in the surrounding area. Employees who donate to this cause receive a special commemorative year 2000 button as souvenir.

Gloria Marquez Sundaresan is an EEO specialist.

QUALITY OF WORK LIFE

Center, CDRH Cooperate in Sponsoring QWL Open House at Corporate

BY SHELLEY JOHNSON AND LYNDA PAPIO

CDER and the Center for Devices and Radiological Health held a joint Quality of Work Life Open House at the Corporate Office Complex on Nov. 10.

Activities included a farmers' market; foot screenings; a visit by a reflexologist and massage therapist; the Combined Federal Campaign; the Parent Warm Line, a service that provides assistance for parents with disciplining their children, self-esteem and school problems; and union representation. There were also informational handouts on work and family programs.

This collaboration between the two centers generated a tremendous amount of positive feedback and was a first of a series of quarterly QWL activities. Additional events and locations will be announced.

Shelley Johnson and Lynda Papio are management analysts in the Office of Management and coordinate the Center's Quality of Work Life Program.

DRUGS IN THE NEWS

New Approvals, Uses for Stroke, Epilepsy, Posttraumatic Stress Disorder

Highlights of recent approvals of new drugs or new uses include treatments for:

- Stroke risk reduction.
- Epilepsy.
- Posttraumatic stress disorder.
- Nail fungus infections.

A new drug that combines two active ingredients—aspirin and dipyridamole—into one pill was approved on Nov. 23 to reduce the risk of stroke for patients who have already had transient ischemic attacks or completed ischemic strokes due to blood clots in the brain.

The pivotal clinical trial of the new drug, which will be marketed as Aggrenox by Boehringer Ingelheim Pharmaceuticals, Inc. of Ridgefield, Conn., was a double-blinded, placebo controlled, 24-month study, referred to as European Stroke Prevention Study 2. The results showed the combination reduced the risk of stroke by 36.8% and the cumulative risk of stroke and death by 24.2% compared to placebo.

Levetiracetam, approved on Dec. 1, is a new epilepsy drug that controls partial onset seizures in adults when used with other epilepsy medications. Partial onset seizures occur when abnormal electrical activity only involves one area of the brain. The drug is chemically unrelated to most currently marketed antiepileptics. The new drug will be manufactured and distributed by UCB Pharma Inc. of Smyrna, Ga., under the trade name Keppra.

Sertraline hydrochloride is the first drug treatment approved for posttraumatic stress disorder. Its effectiveness for treating symptoms of PTSD is based on two multicenter, placebo-controlled, 12-week trials in adults diagnosed with the disorder. The overall positive outcome in these trials appeared to derive from the female patients, with little effect seen in the male subgroups. The new indication for sertraline, marketed as Zoloft by Pfizer Inc. of New York City, was approved Dec. 7.

Ciclopirox, the first topical treatment approved in the United States for the treatment of fingernail and toenail fungus, is a synthetic broad-spectrum antifungal agent that inhibits the growth of dermatophytes, a type of fungus that grows on the skin, hair and nails. Up to 48 weeks of daily applications, weekly trimming by the patient and monthly professional removal of the unattached, infected nail are needed. Ciclopirox, approved Dec. 15, is manufactured by Aventis Pharma Deutschland GmbH of Frankfurt, Germany, and will be marketed under the trade name Penal Nail Lacquer (Ciclopirox) Topical Solution 8%.

Risk Management Workshop Marks Change in Center's Outlook

(Continued from page 1)

described growing public interest in risk management. She explained that the risks of drugs are managed by a system and the principal risk manager is the individual prescriber. Traditional FDA regulatory controls, through labeling and by making sure promotion is balanced, "may have applied when the physician had half a dozen medicines that he or she routinely prescribed and maybe a dozen more used regularly," she said.

"Now there are hundreds of pharmaceuticals. The idea that prescribers should shoulder all the burden themselves is out the window. We are relying on a construct of risk management that is no longer valid."

The first three speakers discussed current concepts in risk management and their application to the health-care setting. Milton Weinstein, M.D., professor of health policy and management at the Harvard University Center for Risk Analysis, discussed the theory and language of risk management. Decision making about using drugs involves making tradeoffs between the probabilities of benefits and risks. These decisions ultimately involve values.

Weinstein described the "ABCs" of risk-benefit. *Absolute risk*, not relative risk, matters. From the public health point of view, increasing the risk of a very rare event 10-fold matters less than a slight rise in risk of a common event. *Baseline risk* for the individual patient matters and depends on each patient's risk factors for disease. The c*onsequence* of events, their seriousness and permanence, matter.

Eric Holmboe, M.D., head of the division of general internal medicine at the Uniformed Services University of Health Sciences, reviewed a variety of studies on the difficulties of communicating risk adequately in the health care setting. "Understanding risk is a complex task that involves objective information and subjective interpretation," he said.

Because most risk and benefit information is derived from population-based studies, probability remains the largest challenge to risk communication. As an example, he said a certain treatment may carry a 4 percent risk of a heart attack. "There's no such thing as 4 percent of a heart attack for a particular patient," he said.

While qualitative expressions of risk may seem more "accessible" to patients, studies reveal that they are subject to wide variations in interpretation. Other challenges with a profound effect on interpreting risk information include:

- The "framing effect" of the context of the presentation.
- "Anchoring bias," in which a person estimates risk from other related events or procedures that are familiar.
- "Availability bias," in which notoriety of the risk plays a role.
- "Compression," in which people overestimate small risks and underestimate large risks.
- "Miscalibration," which involves an overestimation about extent and accuracy of one's knowledge.

Stephen Fried, an investigative journalist from Philadelphia, gave a moving account from his 1998 book, *Bitter Pills*, about adverse reactions to prescription drugs. His investigation was prompted by his wife's severe reaction to one pill of a new antibiotic. He called on CDER to find partners to better manage the known risks from drugs because systemwide improvements are needed.

Five of the Center's medical officers described how risk management concepts are applied in the pre-market review of drugs. **Thomas Laughren, M.D.,** provided an overview, and individual risk management case studies were presented by **Cynthia McCormick, M.D., Randy Levin, M.D., John Feeney, M.D.,** and **Robert Hopkins, M.D.**

Post-market risk assessment featured three presentations. William Lowrance, the former executive director of the International Medical Benefit-Risk Foundation and now a health-policy consultant based in Geneva, presented an overview of the challenges facing regulators in post-market risk assessment and management.

Michael Cohen, a long-time patient safety advocate and president of the nonprofit Institute for Safe Medical Practice located in Huntingdon Valley, Pa., described how his organization conducts a systematic assessment of how and where pharmaceutical packaging, labeling, nomenclature and devices may be vulnerable to confusion. Most medication errors are the result of multiple breakdowns in systems designed to protect patient safety.

Peter Honig, M.D., MPH, deputy director of the Office of Post-Marketing Drug Risk Assessment, discussed the remaining challenges in premarket risk assessment, the sources of injury from drugs and the tools needed to build a comprehensive post-marketing patient safety program.

FDA Commissioner **Jane Henney, M.D.,** opened the second day of the workshop with general remarks on the importance of risk management and her commitment to helping the Center obtain the resources needed for an improved post-marketing safety program.

Nancy Smith, Ph.D., director of OTCOM, described CDER's evolving role in risk management. Before 1995, the Center's effort was product specific and focused almost entirely on the drug's professional labeling. Since then, the product specific information now includes expanded data on the Internet about new molecular entities including the approval letter, labeling text, consumer information, the reviews and any transcripts of advisory committee meetings. The Center communicates general information about drug benefits and risks through the Internet, publications and brochures, stakeholder meetings, exhibits and special campaigns.

Nancy Ostrove, Ph.D., from the Division of Drug Marketing and Advertising, and **Robert Temple, M.D.,** director of the Office of Medical Policy, discussed the Center's risk communications with both health care professionals and patients, including the Center's efforts to provide improved professional labeling. More patient information will be coming, Temple said, because physicians have many patients and little time for each, but each patient has only one patient and a great deal of time.

The reviewers broke into small discussion groups to identify risk management issues in CDER and mechanisms for improvement. Dr. Woodcock shared their findings and commented on them for the workshop finale. Session moderators were Nancy Smith, **Laurie Burke, Debbie Henderson** and **Linda Brophy.**