news along the pike

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CENTER FOR DRUG EVALUATION AND RESEARCH

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INSIDE . . .

PIKE'S CORNERS

Fall Honor Awards recognize striving for excellence

54 individuals, 40 work teams celebrated at ceremony

BY JACKIE BARBER

At the Center's Fall Honor Awards ceremony held Nov. 22 in Gaithersburg, 54 individuals and 40 groups were recognized. Center Director **Janet Woodcock, M.D.,** Deputy Center Director **Steven Galson, M.D.,** and senior managers handed out the awards. The Montgomery County Police Color Guard presented the colors, and Kevin Barber sang the national anthem.

"Our staff continues to exceed all expectations and strive for excellence as evidenced by the wide range of achievements and disciplines represented here today," Dr. Woodcock told the awardees. "A true spirit of innovation and cooperation is apparent at all levels and in every work unit at CDER. Both as individuals and as vital members of work teams, your commitment to CDER's important public health mission is evident in your fine accomplishments."

Rita Thompson, the director of the Division of Management Services in the Office of Management, introduced each award. Office directors provided an explanation of individual achievements, and Thompson read the citations for the individual and team achievements.

The awards were:

FDA Outstanding Service Award

Mark S. Hirsch, M.D.

Active Control Non-Inferiority Trial Design/ Analysis Development Statistics Team: **Hsien-Ming James Hung, Ph.D., Yi Tsong, Ph.D.,** and **Sue-Jane Wang, Ph.D.**

Alosetron Risk Management Team: **Suliman I.**

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FDA initiative seeks to improve product development

FDA announced on Jan. 31 a broad initiative aimed at reducing the time and costs of medical product development and facilitating the introduction of innovative new technologies while maintaining its traditional high standards of consumer protection.

The Agency intends to achieve these goals through new actions in three major areas:

- Identifying the root causes of multiple review cycles and avoiding them when possible through early communication and other steps to improve the quality of new product applications.
- Improving the quality and efficiency of the review process by adopting a quality systems approach to medical product reviews.
- Improving the quality of submissions in new and priority product areas by providing clearer up-to-date guidance for particular diseases and for emerging technologies.

The proposed actions are outlined in a detailed report, *Improving Innovation in Medical Technology: Beyond 2002,* developed by an

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FDA Science Forum to focus on protecting public health

Don't miss the 9th Annual FDA Science Forum, "FDA Science: Protecting America's Health." This premiere scientific event will be held April 24 and 25 at the new Washington Convention Center. The Science Forum, our annual showcase of FDA scientific achievements, is an excellent opportunity to see the role science plays in our regulatory mission and to discuss new scientific trends and regulatory challenges.

Open to the public, the 2003 Forum is designed to bring FDA scientists together with representatives from industry, academia, government agencies, consumers groups and international constituents to explore emerging public health issues and to learn and share knowledge and ideas of the science-based mission of the Agency.

Speakers and panelists will address emerging issues in risk management and assessment, public health initiatives in the aftermath of Sept. 11, 2001, and novel FDA science initiatives.

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JOE'S NOTEBOOK

Black History Month chemistry essay

Norbert Rillieux (1806-1894) was the inventor of the multiple-effect vacuum evaporator, which revolutionized the processing of sugar. Techniques developed by Rillieux have been adopted for the production of any number of heat-sensitive solids and reduced liquids. Rillieux's basic invention and devices based on his process are critical to the manufacture of drugs and other commodities as condensed milk, soaps, gelatins, glues, the recovery of waste liquids in distilleries and paper-making factories, and the processing and production of petrochemicals.

Rillieux was born in pre-Civil War New Orleans as a "free person of color." Like many young men of his social milieu in New Orleans, Rillieux was sent to France to study. Early on he showed an interest in engineering, and by the 1830s he was an instructor at the École Centrale in Paris. He not only understood the principles of thermodynamics and latent heat but also applied that knowledge to the technical needs of the sugar industry.

Sugarcane had become the dominant crop within Louisiana, but the sugar refining process employed at that time was extremely dangerous and very inefficient. Known as the "Jamaica Train," the process called for sugarcane to be boiled in huge open kettles and then strained to allow the juice to be separated from the cane. The juice was then evaporated by boiling it at extreme temperatures, resulting in granules being left over in the form of sugar. It was a dangerous process because workers were forced to transport the boiling juice from one one kettle to another, chancing the possibility of suffering severe burns. It was not only labor -intensive but expensive considering the large amount of fuel needed to heat the various kettles.

Unsuccessful attempts had been made previously to harness the energy of the steam rising from the boiling juice. Rillieux discovered that by using condensing coils in a vacuum chamber it was possible to lower the boiling point of the sugarcane juice by employing a series of three or four closed evaporating pans in which vapor was piped out of each pan to heat the juice in the next, with the vapors in the end going to a condenser. At the same time, pressure in the system was reduced by pumps, which created a partial vacuum. Rillieux's innovation greatly reduced the cost of sugar refining.

Wealthy Louisiana planters quickly understood the significance of Rillieux's discovery. Rillieux was invited back to New Orleans, and in 1843 two planters installed Rillieux's evaporators on their plantations. Three years later, the pair won prizes for producing the best sugar.

Rillieux gained recognition as one of the prime architects of the modern sugar industry. The success of Rillieux's evaporator made him, according to a contemporary, "the most sought after engineer in Louisiana." He acquired a large fortune. But while his invention no doubt enriched sugar planters, Rillieux was still, under the law, "a person of color" who might visit sugar plantations to install his evaporator but who could not sleep in the plantation house.

As the Civil War approached, the status of free blacks deteriorated with the imposition of new laws and restrictions on their ability to move about the streets of New Orleans. Sometime around the start of the Civil War, Rillieux returned to France, where he became interested in Egyptian hieroglyphics. He died in 1894 and was buried in Paris' famous Père Lachaise cemetery.

For Jim Morrison fans: As an educational service for all who work for or do business with the Center, we are pleased to present a special issue of *News Along the Pike* containing all the essays written by **Jim Morrison,** the Center's ombudsman from 1995 to 2003. You can find it at http://www.fda.gov/cder/pike/Special2002a.htm.

news along the pike

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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

Some last thoughts from the old ombudsman, in with the new

BY JIM MORRISON

In this, my final column and the first *Pike* issue of the new year, I'll give you some parting thoughts and introduce my replacement. I could write a book about the changes I have seen in drug regulation since I joined the Agency in 1965. Trying to leave you with some meaningful thoughts in a 700-word column is challenging, but here goes.

In 1965, medicine was very paternalistic. It wasn't uncommon for physicians to tell terminal cancer patients that, "there is always hope." And patients believed them, because they wanted to. The FDA had just been revamped to include effectiveness as well as safety in the evaluation of new drugs, and clinical studies were regulated in the wake of the thalidomide tragedy.

Fundamentally, the system was designed with the FDA acting as a funnel with a filter through which all products must pass before reaching the market. But later that model started to fall apart.

The public became more educated, and the news media began routinely reporting preliminary results of pharmaceutical research. People demanded more candor from their physicians. As they became aware of potential treatments for life-threatening diseases, they realized that they did not have time to wait until the normal drug development process had been completed.

When the AIDS epidemic reached a critical point, its victims became the militant vanguard of patients demanding treatment with drugs based on only preliminary signs of effectiveness and safety. While the FDA adjusted its rules accordingly, the demand for new, inadequately tested treatments increased. Patients learned how to research the medical literature themselves. Soon, patients with no alternatives demanded treatments that had been shown to work only in animals.

The end of the 20th century saw the rapid adoption of the Internet, a new technology with the potential to change society as dramatically as did the printing press and movable type more than 500 years earlier. In a few short years, the Internet went from a means for scientists to communicate to a common forum for international communication. It has changed the rules.

Anyone, from Bangkok to Bimini with a hundred dollars can set up a Web site and accept credit card payments. And as yet, no government has been able to regulate the transcontinental flow of information and products moving with speed and relative anonymity.

The FDA's legal model of a filter preventing dangerous or ineffective drugs from reaching the consumer has been breached. While the legitimate drug industry needs the regulatory framework as much as the FDA needs companies to adhere to it, we cannot ignore the challenges posed by drugs marketed through the Internet.

The key to drug regulation now and in the future is information. Whoever has the most useful and informative Web site will be in the best position to influence the public's health care decisions. CDER has a good Web site now, which is a tribute to the staff who keep it up. However, we need to do much more to make it user friendly and to upgrade its content and timeliness.

The CDER site needs to go beyond the information contained in drug labeling. It needs to include a compendium on drugs and drug usage, perhaps through links to other sites as well, and it needs to explain the risks and benefits of drugs in language that the lay public can understand. That will require multiples of the current resources being put into the site. If CDER does not expend that additional effort; however, other organizations or commercial entities will become the premier sources for information about drugs. That would be unfortunate indeed.

So much for the old Ombudsman. It has been a pleasure to serve CDER in that capacity and in other ways during my career here. **Warren Rumble** has agreed to take over the ombuds duties, at least until the position is advertised and filled permanently. His background as a NIH researcher and nuclear pharmacist, a program manager in CDER and a senior reviewer in the Division of Drug Marketing and Advertising gives him a good foundation for success. Most importantly, he has a warm and calm personality, an invaluable asset to an ombudsman.

I know you will give Warren the same generous cooperation you have given me, and I wish him and CDER all the best in the future.

Jim Morrison's last day as CDER ombudsman was Jan. 3.

Pike's Puzzler: Watch your spelling

BY TONY CHITE, P.D.

1. One of these words is a male gland, while the definition of the other is "lying face down." Which word is the male gland?

a. prostate
b. prostrate

2. Which of these words is the correct spelling for "the visible flash of light during a thunderstorm"?

a. lightening
b. lightning
c. litening

3. Which of the following is the correct spelling for "to have awareness of one's self"?

a. conscius
b. conscience
c. consious
d. conscious

4. Tachycardia and bradycardia are examples of the heart in an abnormal:

a. rhthmn
b. ryhthmn
c. rhythm
d. rhythmn

5. The domed building in Washington , D.C., where Congress meets is:

a. the U.S. Capitol
b. the U.S. Capital
c. the U.S. Capitle

Key: 1a; 2b; 3d; 4c; 5a.

Tony Chite is a CSO and pharmacist with the Division of Information Disclosure Policy.

BlackBerry MetaMessage application to allow viewing attachments

BY EBE UGWU

The Office of Information Technology, in its latest effort to provide advanced functionality in the use of your BlackBerry, approved the rollout of MetaMessage.

MetaMessage is an application that will allow you to read attachments and Web pages, look up addresses in the FDA Global Address List and send e-mail messages, attachments and Web pages to print on a fax machine all from your BlackBerry.

MetaMessage has received excellent feedback from current users. So, if you own a BlackBerry, jazz it up with MetaMessage by visiting http://cdmail/Blackberry/ or contact the CDER Helpdesk for more information.

Global Address List changes

BY JOE NEUBAUER

The HHS chief information officer, in order to implement changes that reflect the secretary's one department vision, has directed all the department's operating divisions to improve e-mail consistency and interoperability across HHS. This directive changed the way that names are displayed in the e-mail directory. The change is being implemented throughout the department's agencies.

From an FDA perspective, names in the e-mail directory, also referred to as the Global Address List or GAL, can be divided into two categories: FDA names and non-FDA names. Prior to the change, non-FDA names were seen in the directory prefixed with "HHS-." We removed this prefix to provide a more uniform look to the directory as seen from any part of the department.

Non-FDA names are now be intermixed throughout the directory. Before the change, the non-FDA names were grouped together because of the HHS- prefix.

When you enter addressees by typing a portion of a person's first or last name, you will need to use more caution to ensure that you select the correct name. Before the change, if you typed "Aaronson" in the TO field of a message, only one name would match (Wendy Aaronson). When the HHS prefix was removed, Aaronson now matches three names (Wendy, Kenneth and Robert).

How do I tell who is who?

Even though we are removing the HHS prefix from non-FDA names, these names will still have other identifiers to help you determine if they are part of the FDA or not. First, each non-FDA name will have the person's operating division included in parentheses after the name. For example: "Aaronson Robert (PSC)."

Second, when you are presented with multiple matches, all non-FDA names will have an icon of a globe displayed to the left of the name. Again using the Aaronson example, when the three names are displayed, Kenneth's and Robert's names have a globe icon and Wendy's does not.

If you've added HHS individuals from the Global Address List to your personal address book or contacts you will not need to change them.

Remote access upgrades

BY JOE NEUBAUER

When you connect to the CDER network using a Secure Remote Access Session, your PC is connected to the network in a similar way as the PC in your office. You have access to all of the same systems and resources. The main difference is that the speed at which you can communicate is limited by the capabilities of the telephone system.

When you access resources such as your e-mail, the copy of Outlook running on your PC is talking directly to the e-mail server and thus the two are exchanging data directly. In some cases, the amount of data that needs to be transferred between the mail server and Outlook can be large.

When you are connected at slower speeds, as you may have experienced when using a RAS or SRAS system, the delay opening e-mail can be a problem.

To help mitigate this, OIT is working with the Network Control Center to make available a service called Citrix.

Citrix provides a "remote control" capability. When you connect to a Citrix server and run Outlook, Outlook is running on a server in an FDA data center, not on your PC.

The Citrix server transmits an image of what is happening in Outlook to your PC's monitor and likewise your PC transmits mouse and keyboard commands to the Citrix server so that you can "remote control" Outlook.

The links between the systems work like this: E-Mail server <--> Citrix server <--> Your PC.

All of the "big" data, like attachments, only move between the e-mail server and the Citrix server, which communicate at the same speeds as your office PC. Only screen, mouse and keyboard data move between the Citrix server and your remote PC.

Screen, mouse and keyboard data is much easier to compress and transmit over a slower connection compared to the much larger data that is usually received in e-mail.

One thing you may be thinking at this point is: "Will someone be able to see what I'm doing in Outlook?" The answer is no! Even though this service works using a remote control principle, there is no actual monitor running on the Citrix server that displays what is happening during your connection.

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February OIT Training

Tuesday	Wednesday	Thursday
18 Outlook Email 9-12 (P) Outlook Calendar Class is full (P) JMP Session II 1-4 (C)	19 DSS 9-12 (C) Outlook Calendar 9-12 (P) DFS 1-4 (C) Excel 1-4 (P)	20
25 NEST 9-12 (C) NEDAT 1-4 (C)	26 PowerPoint Intro 9-12 (P) PowerPoint Charts and Templates 1-4 (P)	27

Key: Corporate Blvd (C), Park Building (P)
Go to http://OITWeb to access training registration and resources.

FDA's physician survey on DTC Rx drug ads shows health benefits

BY KATHRYN J. AIKIN, PH.D.

Preliminary analysis of an FDA survey of 500 physicians about the impact of direct-to-consumer advertising for prescription drugs on the doctor-patient relationship confirm that DTC advertising, when done correctly, can serve positive public health functions.

Forty-one percent of those surveyed reported that DTC advertising had a beneficial effect on their interactions with patients, and 18 percent reported that DTC advertising caused problems.

The physicians surveyed included 250 general practitioners and 250 specialists drawn from the American Medical Association masterfile.

The benefits include increasing patient awareness of diseases that can be treated and prompting thoughtful discussions with physicians that result in needed treatments being prescribed—often, not the treatment in the DTC advertisement. Problems included time spent correcting misconceptions.

Most surveyed physicians view DTC advertisements as one of many factors that affect their practice and their interactions with patients, both positively and, in some respects, negatively.

Highlights of the survey include:

- Seventy-three percent of all physicians surveyed strongly or somewhat agreed that patients who saw a DTC ad asked more thoughtful questions during their visits.
- Seventy-two percent thought that DTC ads made their patients more aware of possible treatments.
- Fifty-eight percent of the physicians also thought that DTC ads made their patients more involved in their healthcare.
- Physicians also felt they had to provide additional information to patients beyond what patients retained from the DTC advertising.
- About 75 percent of physicians believed that DTC ads cause patients to think the drug works better than it did.
- Sixty-one percent of physicians felt some pressure to prescribe a drug when they were asked about a specific brand name drug.
- However, only 8 percent felt very pressured to prescribe the specific brand name drug when asked about it. Physicians listed a number of reasons why they did not prescribe the drug the patient requested, including: a different drug was more appropriate, there were side effects the patient did not know about or a less expensive drug was available.
- One effect of DTC ads was to help educate patients about their health problems and to provide greater awareness of treatments. When a patient asked about a drug, 88 percent of the time they had the condition that the drug treated. And 80 percent of physicians believed patients understood what condition the drug treats.
- Moreover, doctors believe that patients understand they need to consult a health care professional about appropriate treatment: 82 percent of physicians believe patients understand very well or somewhat that only a doctor can decide if the drug is right for the patient.
- This is important, because only 40 percent of physicians believe that patients understood very well or somewhat well the possible risks and negative effects of an advertised drug from the DTC ad alone.

The results show that DTC ads can and do help increase patient awareness about the availability of effective treatments for their health problems.

However, FDA's DTC policies must help prevent potential misperceptions about benefits and risks of the advertised treatment.

Any actual prescribing decision should be based on careful consultation between a patient and his or her health professional to make sure that all relevant information is considered.

FDA will continue to scrutinize DTC ads closely to ensure that all essential information is communicated as clearly as possible, as outlined in our current policy. In addition, FDA will continue its comprehensive evaluation of DTC advertising and its impact on public health and FDA's policies and guidance.

This is the third survey conducted by FDA to help the agency assess the impact of DTC advertising. FDA will continue to analyze these data. The Agency will continue its comprehensive evaluation of DTC advertising and its impact on public health, to ensure that current DTC policies maximize the positive benefit that DTC advertising can play in the public health arena.

Kathryn J. Aikin, who analyzed the results of the survey, is a social scientist in CDER's Division of Drug Marketing, Advertising and Communications and was a member of the team responsible for the design of the survey. Her analysis is available at http://www.fda.gov/cder/ddmac/globalsummit2003/index.htm.

Remote access users to see improved Outlook performance

(Continued from page 4)

The Citrix servers allow between 500 and 1,000 people to connect and run applications, such as Internet Explorer, Outlook, Adobe and Microsoft office.

Other applications will be available in the future.

The number of users who can connect varies depending on the demands of the software they are using.

Network upgrades

BY RICH JOHNSON

OIT is moving forward again on the Network infrastructure upgrades. The next part of the upgrades is to move all of the buildings in the Rockville area to gigabit Ethernet. This will increase speed between these buildings and Parklawn. Each building will have two separate connections back to the Parklawn building. This will provide for redundancy.

The Montrose II building has already been connected using gigabit Ethernet. This is a new building into which CDER staff from the Office of Compliance has moved. The work on the rest of the locations should be starting on the maintenance weekend in March. Look for e-mail messages from OIT on the exact dates and locations to be changed.

HHS lists 12 drugs for government-sponsored pediatric testing

HHS Secretary **Tommy G. Thompson** on Jan. 21 named 12 commonly prescribed drugs that need to be tested for use in children.

He said government-supported tests of the drugs will begin this year, with up to $25 million available to launch the tests in the current fiscal year and up to $50 million for testing to be included in the president's fiscal year 2004 budget proposal.

The testing is called for in the Best Pharmaceuticals for Children Act, which was signed into law last year. The law provides for the National Institutes of Health to sponsor pediatric tests of certain drugs already approved for marketing but either never tested or not fully tested specifically for their effects in children.

The list identifies the dozen highest-priority drugs needing pediatric testing.

"Children often react differently to drugs than adults do," Thompson said. "The drugs we are naming today have long been approved for marketing and are often prescribed for children, yet they have either not been tested at all in children or have not been tested in all age groups of children where they are used. We need to conduct testing now to fully understand the effects of these medications in our children."

The list of drugs was developed by the National Institute of Child Health and Human Development with FDA and experts in pediatric research. The list identifies gaps in drug use information for which studies would be needed for specific ages of children or diseases.

The list, which will be updated each year, includes:

- *Azithromycin,* an antibiotic used to treat many different types of infections.
- *Baclofen,* a muscle relaxant used to treat the spasms and tightness of muscles in patients with cerebral palsy.
- *Bumetanide,* a diuretic that causes the kidneys to get rid of excess water and salt from the body.
- *Dobutamine,* a drug that stimulates the heart and is used in critically ill patients.
- *Dopamine,* a drug that is used to treat shock in critically ill patients.
- *Furosemide,* a diuretic that causes the kidneys to get rid of excess water and salt from the body.
- *Heparin,* a drug used for the prevention and treatment of harmful clots in the blood vessels)
- *Lithium,* a drug used for the treatment for bipolar disorder -- extreme mood changes from depression to mania.
- *Lorazepam,* a drug used for the treatment for acute seizures and long-term sedation in the intensive care unit.
- *Rifampin,* a drug used in combination with other medications to treat tuberculosis, and to treat carriers of certain meningitis-causing bacteria.)
- *Sodium nitroprusside,* a drug used to reduce blood pressure in critically ill patients.
- *Spironolactone,* a drug used as part of a regimen to prevent loss of potassium.

Each drug will undergo testing that could last several months to several years, depending on the type of testing needed. FDA will evaluate the test results, share them with the pediatric community so that doctors and parents can make better treatment decisions for children, and make appropriate changes to drug labels. NICHD will oversee the testing process, consulting closely with other NIH institutes and FDA.

Integral to NIH's testing effort, FDA will work with NIH, industry and the pediatric community to determine the specific research needed to improve pediatric-prescribing information on both the drugs on the list and others prescribed for children but needing further testing.

FDA will spend a total of $6.6 million this year to fund its responsibilities under the law. The president's budget proposes increasing this to $11.5 million in fiscal year 2004. Most of the listed drugs are no longer under patent or have marketing exclusivity and, therefore, are not the property of any single drug firm. For this reason, the new law provided for government sponsorship of these pediatric drug trials.

In addition to requiring the NICHD and FDA to compile the list of drugs, the Best Pharmaceuticals for Children Act reauthorized pediatric exclusivity. This economic incentive provides extended protection from market competition for pharmaceutical companies that conduct pediatric studies requested by FDA.

In the meantime, for pediatric testing of new drugs, HHS announced last month that it will seek new legislation from Congress to clearly establish FDA's authority to require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials on new drugs and biologics (Nov.-Dec. *Pike).* Legislative authority would be pursued because it was quicker and more decisive than legal appeals. FDA earlier asserted its right to require such tests, but the U.S. District Court for the District of Columbia ruled against the agency last October.

Safety changes for labeling of estrogen announced

On Jan. 8, FDA announced safety changes to labeling of all estrogen and estrogen with progestin products for use by postmenopausal women.

These changes reflect FDA's analysis of data from the Women's Health Initiative study, a landmark study sponsored by the National Institutes of Health.

Results from the study have shown that postmenopausal women taking estrogen plus progestin have an increased risk of heart attack, stroke, breast cancer and blood clots.

Changes include a boxed warning that reflects new risk information and changes to the approved indications to emphasize individualized decisions that appropriately balance the benefits and the potential risks of these products.

FDA at the end of January issued updated guidances for manufacturers of estrogen and estrogen with progestin products regarding labeling and development of new products for use in postmenopausal women.

Complete information is available on CDER's Web site at http://www.fda.gov/cder/drug/infopage/estrogens_progestins/default.htm.

FDA approves pyridostigmine under animal efficacy rule

FDA on Feb. 5 announced approval of pyridostigmine bromide to increase survival after exposure to Soman "nerve gas" poisoning. The product is approved for combat use by U.S. military personnel.

Pyridostigmine bromide is the first drug approved under an FDA rule that allows use of animal data for evidence of the drug's effectiveness for certain conditions when the drug cannot be ethically or feasibly tested in humans.

Frequently referred to as the "animal efficacy rule," the regulation became effective June 30 and is an important component of FDA's efforts to make medical countermeasures available to treat or prevent the effects of biological and chemical agents. The "animal efficacy rule" enabled FDA to approve pyridostigmine bromide to increase survival from Soman poisoning despite the impossibility of ethically conducting human studies on the effectiveness of the drug.

The nerve agent Soman causes loss of muscle control and death from respiratory failure. Evidence of the effectiveness of pyridostigmine bromide as a pretreatment for exposure to Soman was obtained primarily from studies in monkeys and guinea pigs.

This evidence shows that administration of the drug before exposure to Soman, together with atropine and pralidoxime given after exposure, increases survival. FDA believes that, based on the animal evidence of effectiveness, pyridostigmine bromide is likely to benefit humans exposed to Soman.

The Agency's safety assessment is based on long-term use of pyridostigmine bromide, first approved by FDA in 1955, to treat the neuromuscular disease myasthenia gravis. The Department of the Army submitted data from multiple controlled trials and uncontrolled clinical experience demonstrating pyridostigmine bromide is well-tolerated at the doses intended for military use. The dose used for myasthenia gravis is higher than the dose used for pretreatment to protect against Soman.

To use this potentially lifesaving drug correctly, military personnel must carefully follow instructions and use the drug only under specific circumstances. For example, if U.S. troops faced the threat of exposure to Soman, they would be given instructions to take pyridostigmine bromide every eight hours prior to the anticipated exposure.

Soldiers will be warned that the drug is not effective and should not be taken at the time of or after exposure to Soman.

The FDA press release, approval letter, label and questions and answers can be found at http://www.fda.gov/cder/drug/infopage/Pyridostigmine_Bromide/default.htm.

Project BioShield proposes FDA authorizing promising treatments in crises

In his January 28 state of the union address, President Bush proposed Project BioShield—a comprehensive effort to develop and make available modern, effective countermeasures against biological and other dangerous agents.

This major cooperative effort will be a joint activity of the new Department of Homeland Security and the Department of Health and Human Services.

The president's Project BioShield program will:

- *Make promising treatments available quickly for emergencies:* Under Project BioShield, FDA would have the ability to make new and promising treatments still under development available quickly in emergency situations—potentially saving many more lives than treatments otherwise available today.
- *Ensure resources to develop next-generation countermeasures:* The president's plan would create a special secure spending authority to pay for the delivery of "next-generation" medical countermeasures. Over the next 10 years, almost $6 billion will be available to purchase new countermeasures, including therapies for smallpox, anthrax and botulinum toxin. Additional funds will be available to produce and purchase countermeasures for other dangerous agents, such as Ebola and plague, once safe and effective treatments are developed.
- *Expand research and development:* Project BioShield would expand the ability of the National Institutes of Health to speed research and development on medical countermeasures based on the most promising recent scientific discoveries.

More details about Project BioShield are available on the White House Web site at http://www.whitehouse.gov/news/releases/2003/02/20030203.html.

Center seeks counterterror NDAs for Prussian blue

As part of CDER's continuing effort to foster the development and availability of countermeasures to terrorist attacks, the Center examined the evidence for Prussian blue, a mineral compound also known as ferric hexacyanoferrate (II) as a countermeasure for exposure to radioactive elements that may be released from terrorist attacks using a dirty bomb.

Since the 1960s, it has been used investigationally as an orally ingested drug to enhance the excretion of isotopes of cesium and thallium from the body by means of ion exchange. CDER reviewed the available data and literature, determined that Prussian blue is safe and effective for this indication and recently published this finding in order to encourage manufacturers to submit marketing applications.

Because the Center has already completed the safety and efficacy review work, applicants need only to submit the chemistry information for the Prussian blue product they make. To facilitate the process, the Agency has prepared draft labeling and has published a guidance document on how to submit these applications. More information is available on CDER's Web site at http://www.fda.gov/cder/guidance/5506fnl.doc.

Fall Honor Awards Ceremony recognizes Center's drive for excellence

(Continued from page 1)

Al-Fayoumi, Jane A. Axelrad, Julie G. Beitz, M.D., Allen D. Brinker, M.D., Jason Brodsky, Bronwyn E. Collier, Anne Corken-Mackey, R.Ph., Heidi Forster, J.D., Hugo E. Gallo-Torres, M.D., Lahn Green, R.Ph., Maureen A. Hess, David Hoberman, Ph.D., Florence Houn, M.D., M.P.H., Donna Katz, J.D., Joyce A. Korvick, M.D., Scheldon Kress, M.D., Karen J. Lechter, Ph.D., Paul E. Levine Jr., R.Ph., Zili Li, M.D., Thomas J. Permutt, Ph.D., Toni D. Piazza-Hepp, R.Ph., Victor F. Raczkowski, M.D., and **Crystal L. Rice.** PHS companion award nomination: **CAPT David B. Banks, LT Marci C. Kiester, LCDR Mary E. Kremzner** and **CAPT Thomas H. Perez.**

Personnel Operations Branch, DMS/OM: **Pheobe A. Brooks, Joseph M. Cejmer, Jennifer G. Chung, Diana L. Dycus, Patricia L. Gathers, Mary F. Goodson, Lucinda R. Hall, Angela N. Harris, Blossom M. Harrison, Cynthia A. Hart-Burge, Ellen A. Johnsey, Leah M. Mader, Sharon L. Miller, Kristin L. Montgomery, Denise M. Riggs, Ruth M. Skinner, Joyce A. Seawright, Margie Stewart-Rivers, Tabitha L. White, Jessica V. Wilcox**

Schering Injunction Compliance Review Team: **Frederick W. Blumenschein, Joseph C. Famulare, Diane J. Kelley** and **Barry Rothman.**

FDA Leveraging and Collaboration Award

Timothy M. Mahoney

Rajeshwari Sridhara, Ph.D.

International Visitors Facilitation Team: **Marie Dromerick** and **Barry W. Poole.** PHS companion award nomination: **LCDR Mary E. Kremnzer** and **CAPT Justina A. Molson.**

FDA Quality of Work Life Award

Deborah J. Henderson

OTCOM QWL Team: **Debra L. Rose** and **Jennifer L. Snellings.**

PHS Commendation Medals

CDR Edward D. Bashaw

LCDR Sean K. Bradley

CAPT Lillian Gavrilovich

CDR Carol A. Holquist

CDR Karen G. Hirshfield

CAPT David G. Orloff

CDER Special Recognition Award

Joseph F. Contrera, Ph.D.

Ruthanna C. Davi

Cindy M. Kortepeter, Pharm.D.

Cynthia G. McCormick, M.D.

Nashed E. Nashed, Ph.D.

Judith A. Putz

Jenny H. Zheng, Ph.D.

Casodex Review Team: **Rajiv Agarwal, Ph.D., Jeanine A. Best, Maryann Gordan, M.D., David Hoberman, Ph.D., Alexander W. Jordan, Ph.D., Scott E. Monroe, M.D., Nancy S. Scher, M.D., Daniel A. Shames, M.D., Michael E. Welch, Ph.D.,** and **Peiling Yang, Ph.D.**

Clarinex Pediatric Safety Team: **Badrul A. Chowdhury, M.D., Ph.D.,** and **Sandra Suarez-Sharp, Ph.D.**

Dutasteride Review Team: **Sayed Al Habet, Ph.D., George S. Benson, M.D., Jeanine A. Best,, Barbara S. Chong, Jennifer Fan, Evelyn R. Farinas, R.Ph., Maryann Gordon, M.D., Mark S. Hirsch, M.D., David Hoberman, Ph.D., Alexander W. Jordan, Ph.D., Margaret Kober, David T. Lin, Ph.D., Karl K. Lin, Ph.D., Laurie L. McLeod-Flynn, Ph.D., Ameeta Parekh, Ph.D., Bryan S. Riley, Ph.D., Jean Salemme, Ph.D.,** and **Daniel A. Shames, M.D.**

Webmasters Subcommittee of the Support Staff Coordinating Committee: **Dannette M. L. Alpern, Lisa Champion, Velma L. Cunningham, Juanita I. Fastman, Linda C. Hukle, Myrna-Yvette King, Susan H. O'Malley, Dawn M. Reid, Christine Shipe, Barbara J. Townsend** and **Krista C. Yazdani.**

Center Director's Special Citation

Karen J. Lechter, Ph.D.

CDER Administrative/Program Management Excellence

Teresa L. Bushway

Tammy Grimm

Tina M. Hamilton

Patricia L. Littleton

John B. Schupp

Barbara E. Shekitka

Office of Pediatric Drug Development Administrative Team: **James L. Angel, Pilar A. Martinez, Raya S. McCree** and **Karen D. Smith.**

CDER Excellence in Communication Award

Margaret E. Brower, Ph.D.

Ted J. Guo, Ph.D.

John Leighton, Ph.D.

Lilliam A. Rosario, Ph.D.

Jonthan K. Wilkin, M.D.

Division of Drug Information Team Leaders: **Brenda J. Kiliany, Pharm.D.** PHS companion award nomination: **LCDR Mary E. Kremzner**

Drug Substance and Drug Product Specification Workshop Working Group: **Craig M. Bertha, Ph.D., Chi-wan Chen, Ph.D., Yuan-yuan Chiu, Ph.D., Jon E. Clark, Eric P. Duffy, Ph.D., Bonnie B. Dunn, Ph.D., June S. Ewing, Allan H. Fenselau, Ph.D., Ravi S. Harapanhalli, Ph.D., Martha R. Heimann, Ph.D., Charles P. Hoiberg, Ph.D., Richard T. Lostritto, Ph.D., Dale L. Koble, Ph.D., Mehul U. Mehta, Ph.D., Stephen Miller, Ph.D., Linda L. Ng, Ph.D., Guiragos K. Poochikian, Ph.D., Nancy B. Sager, Norman R. Schmuff, Ph.D., Alan Schroeder, Ph.D., John E. Simmons, Ph.D., John L. Smith, Ph.D., Kasturi Srinivashachar, Ph.D., Rajendra Uppoor, Ph.D.,** and **Duu-Gong Wu, Ph.D.**

Executive Operations Staff: **Christine M. Bechtel, Rose E. Cunningham, Anne M. Henig, Maureen A. Hess, Vikki S. Kinsey, Coralee G. Lemley, Theresa M. Martin** and **Mary L. Ortuzar.**

KI Antidote Preparation Team: **Carol S. Assouad, Patrick E. Clarke, Joanne M. Holmes, Ajaz S. Hussain, Ph.D., Theresa M. Martin, Kathrin L. McConnell, Nancy L. Muir, Francis R. Pelsor, Pharm.D., R.Ph.,** and **Sally Winthrop.**

OGD Good Review Practices Executive Summary Development Team: **Upinder**

(Continued on page 9)

Wide range of achievements, disciplines recognized by awards

(Continued from page 8)

S. Atwal, Ph.D., Sema Basaran, Ph.D., Rosario D'Costa, Ph.D., Lynne A. Ensor, Ph.D., John D. Franolic, Ph.D., Kenneth J. Furnkanz, Ph.D., Ruth Ganunis, Ph.D., Robert W. Trimmer, Ph.D., Tao-Chin L. Wang, Ph.D., and **Kathy P. Woodland-Outlaw.**

Systems Based Compliance Program Presentation/Coordination Team: **Frederick W. Blumenschein, Nicholas Buhay, Robert C. Coleman, Erik N. Henrikson, Susan F. Laska, Erin D. McCaffery, Maridalia Torres Irizarry** and **Rebecca Rodriquez.**

Team for Assuring the Safe Use of Albuterol: **Sandra L. Barnes, Gary J. Buehler, R.Ph., Deborah J. Henderson, Colette C. Jackson, Claudia B. Kawoski, Pharm.D., Marianne C. Mann, M.D., Theresa M. Martin, Guiragos K. Poochikian, Ph.D., Eugene J. Sullivan, M.D., Joyce P. Weaver, Pharm.D.,** and **Robert L. West, R.Ph.** PHS Unit Commendation: **CAPT Timothy W. Ames, LT Peter Chen, LCDR Michelle Dillahunt** and **CAPT Joslyn R. Swann.**

CDER Information Technology Excellence

Melissa L. Bates

James S. Black

Janet L. Gentry

DAIDP OIT-DIMS Team: **Monif Alqarshi** and **Hartsell L. Whitacre Jr.**

Web Document Delivery System Implementation Team: **Sylvia A. Bullock, Wendy W. Cheng, Nichelle Cherry, Carol Knoth Lytle, R.Ph., Kathrin L. McConnell, Monica A. Unger** and **William B. Woodard Jr., Ph.D.**

CDER Leadership Excellence Award

Jonca C. Bull, M.D.

Gang Chen, Ph.D.

Kim M. Colangelo

Lynne A. Ensor, Ph.D.

Karen M. Higgins, Sc.D.

Florence Houn, M.D.

Robert O. Kumi, Ph.D.

See Yan Lam, Pharm.D., Ph.D.

Sue-Chih H. Lee, Ph.D.

Hasmukh B. Patel, Ph.D.

Kasturi Srinivasachar, Ph.D.

CDER Excellence in Mentoring

Tarek Hammad, M.D.

Judith G. Schupp

Binh C. Ta

CDER Project Management Excellence Award

Jennifer L. Mercier

CDER Support Staff Excellence Award

Kimberly A. Campbell

Amiee L. Flook

Eda E. Howard

Linda C. Hukle

Patricia A. Johnson

LaVaughn M. Wilbur

CDER Team Excellence Award

Active Pharmaceutical Ingredient Team: **Susan Jenney, Anjanette P. Smith, Duckhee Y. Toler, Benjamin J. Westenberger** and **Anna M. Wokovich.**

CDER Outlook Implementation Training Team: **Heather A. Chafin, Lana G. Kostecka** and **Nancy J. Shermer.**

Chemistry Review Teams co-located with the Division of Reproductive and Urologic: **Rajiv Agarwal, Ph.D., Jila H. Boal, Ph.D., Swapan K. De, Ph.D., David T. Lin, Ph.D., Amit K. Mitra, Ph.D., Moo-Jhong Rhee, Ph.D., Jean Salemme, Ph.D.,** and **Suong T. Tran, Ph.D.**

DAIDP Supplemental Review Team: **John J. Alexander, M.D., James G. Blank, Ph.D., David C. Bostwick, Alma C. Davidson, M.D., Maureen P. Dillon-Parker, Elizabeth A. Duvall-Miller, Frances V. LeSane, Judith R. Milstein, David B. Ross, M.D., Susmita Samanta, M.D., Albert T. Sheldon, Ph.D., Harold B. Silver** and **Janice M. Soreth, M.D.** PHS Unit Commendation: **CAPT Lillian Gavrilovich** and **LTJG Raquel A. Peat.**

Division of New Drug Chemistry III Chemists co-located with Division of Special Pathogen and Immunologic Drug Products: **Gene W. Holbert, Ph.D., Dorota M. Matecka, Ph.D., Norman R. Schmuff, Ph.D.,** and **Mark R. Seggel, Ph.D.**

Division of Pharmaceutical Evaluation II Exposure-Response Group: **Suliman I. Al Fayoumi, Ph.D., Sang M. Chung, Ph.D., Suresh Doddapaneni, Ph.D., Venkateswa R. Jarugula, Ph.D.,** and **He Sun, Ph.D.**

IND Reform-Chemistry, Manufacturing and Controls Working Group: **Raman K. Baweja, Ph.D., Yuan-yuan Chiu, Ph.D., Charles P. Hoiberg, Ph.D., Stephen K. Moore, Ph.D., Nancy B. Sager, Ph.D., Eric P. Sheinin, Ph.D.,** and **Toy Ping C. Taira.**

Matulane Review Team: **LT Sean K. Bradley, John Z. Duan, Ph.D.,** and **Cheng Yi Liang, Ph.D.**

Office of Drug Safety IMS Health Process Improvement Team: **Jeanine A. Best, Katrina S. Garry, Martha L. O'Connor, Carol A. Pamer, R.Ph., Judy A. Staffa, Ph.D., R.Ph.** PHS Unit Commendation: **CAPT George D. Armstrong Jr.** and **CAPT Joslyn R. Swann.**

Office of Drug Safety New Drug Utilization Resources Team: **Allen D. Brinker, M.D., Min C. Chen, R.Ph., Katrina S. Garry, Gurminders J. Khalsa, Cynthia J. Kornegay, Ph.D., Zili Li, M.D., M.P.H., Carolyn A. McCloskey, M.D., M.P.H., Parivash Nourjah, Ph.D., Martha L. O'Connor, Carol A. Pamer, R.Ph., Marilyn R. Pitts, Pharm.D., Paul F. Reinstein, Leslie L. Saveland, Judy A. Staffa, Ph.D., R.Ph.,** and **Lynette Swartz.** PHS Unit Commendation: **CAPT Joslyn R. Swann.**

Office of Generic Drugs Productivity Measures Team: **Raymond L. Brown, James M. Fan, Florence S. Fang, Shing Hou Liu, Michael Smela Jr., Glen J. Smith** and **Ruth A. Warzala.**

Patient Prescription Drug Information Advisory Committee: **Melissa L. Bates, Christine M. Bechtel, Jeanine A. Best, Kathleen F. Bongiovanni, Karen J. Lechter, Ph.D., Melodi McNeil, R.Ph., Ellen R. Tabak, Ph.D., M.P.H.,** and **Kimberly L. Topper.** PHS Unit Commendation: **CAPT Thomas J. McGinnis, CAPT Thomas H. Perez, CDR Anne E. Trontell**

Peroxisome Proliferator-activated Recep-

(Continued on page 10)

OCPB SCIENCE DAY

Clinical pharmacologists focus on appropriate dosing issues

BY RAY BAWEJA, PH.D., VENKAT JARUGULA, PH.D., SOPHIA ABRAHAM, PH.D., SANDRA SUAREZ, PH.D., ABIMBOLA ADEBOWALE, PH.D., CHARLES BONAPACE, PHARM D., AND LARRY LESKO, PH.D.

The 11th Science Day sponsored by the Office of Clinical Pharmacology and Biopharmaceutics enthusiastically celebrated the theme "Optimizing Dose" on Nov. 1. Events included:

- The keynote address from a best-selling author on dose optimization.
- Presentation of new research on post-marketing safety-related dose changes for NMEs approved 1980-1999.
- Six podium and 16 poster presentations from OCPB staff.
- An entertaining and educational science team game.

Keynote address

Jay S. Cohen, M.D., the keynote speaker, gave his presentation on "Dose Optimization and Preventing Adverse Events: A Clinical Physician's Perspective on Improving Safety." He is the author of the best-selling book, *Over Dose: The Case Against The Drug Companies,* published in October 2001. He is an associate professor of family and preventive medicine and of psychiatry at the University of California at San Diego.

Dr. Cohen has been an active researcher in the area of adverse reactions in drug research, FDA regulation and physician's methods that have contributed to the serious problem of drug safety. He has been interviewed by major newspapers about his book. He is an appealing speaker and very good at presenting his case to both the scientific community and to the lay public.

In his book, he maintains that the recommended doses found in FDA approved labeling are too high for many people and are causing many unnecessary adverse reactions. Drug reactions in hospitals are among the nation's leading causes of death, killing more than 100,000 Americans every year. Dr. Cohen says the "side effect epidemic" causes many people—as high as 50 percent of those on blood-pressure medication—to discontinue treatment.

In his book, Dr. Cohen attributes the problem not only to poor research on the part of the drug companies but also to their effort to create easy, one-size-fits-all dosages that both appeal to doctors and produce artificially inflated effectiveness statistics.

He began his presentation at Science Day by mentioning that the most important piece of medical writing is the package insert. He said a physician assumes that it contains all the useful information he or she needs to prescribe a drug accurately and, particularly, that the dose rec-

(Continued on page 11)

54 individuals, 40 work teams honored at Fall Honor Awards Ceremony

(Continued from page 9)

tor Agonist Working Group: **Hae-Young Ahn, Ph.D., Fred K. Alavi, Ph.D., John B. Colerangle, Ph.D., James T. Cross, Jeri D. El-Hage, Ph.D., Zhaolong Gong, Ph.D., David J. Graham, M.D., Lanh Green, M.P.H., Steven B. Johnson, Ph. D., Elizabeth A. Koller, M.D., William A. Lubas, M.D., Joy D. Mele, Robert I. Misbin, M.D., Stephen K. Moore, M.D., David G. Orloff, M.D., Lee-Ping Pian, Ph.D., Herman J. Rhee, Ph.D., Dragos G. Roman, M.D., Dragos G. Roman, M.D., J. Todd Sahlroot, Ph.D., Bruce V. Stadel, M.D., Jena M. Weber, Da Lin Yao, Ph.D., Xavier J. Ysern, Ph.D.,** and **Joanna K. Zawadzki, M.D.**

Pleconaril Review Team: **Narayana Batula, Ph.D., Cynthia A. Bigger, Ph.D., James G. Farrelly, Ph.D., Russell D. Fleischer, M.D., Lesley-Anne Furlong, M.D., Zi Qiang Gu, Ph.D., Thomas S. Hammerstrom, Ph.D., Katherine A. Laessig, M.D. Stephen Miller, Ph.D., Julian J. O'Rear, Ph.D., Kellie S. Reynolds, Pharm.D., Guoxing Soon, Ph.D., Kathleen Whitaker, Ph.D.,** and **Jenny H. Zheng, Ph.D.** PHS Unit Commendation: **LT Destry M. Sillivan,**

Post-Marketing Commitments Development Team: **Gary M. Anderson, Sheila K. Andrew, Mary L. Guilderson, Cheryl J. Marshall, Robert L. Reinwald, Kathy Smith, Binh C. Ta, Jennifer A. Wagner** and **Jerry Yokoyama.**

Potassium Iodide Evaluation Team: **James F. Brower, Lucinda F. Buhse, William H. Doub, Joseph Famulare, Pat Alcock Lefler, Terra G. Lipe, John C. Reepmeyer, Larry K. Revelle, Anjanette P. Smith, Kimberly D. Story, Duckhee Y. Toler, Benjamin J. Westenberger** and **Anna M. Wokovich.**

Pulmonary Inhalation Products Assurance Post 9-11 Team: **Sandra L. Barnes, Ladan Jafari, Robert J. Meyer, M.D., Michael J. Verdi.** PHS Unit Commendation: **CAPT Harvey A. Greenberg, CDR Valerie E. Jensen** and **LCDR Craig Ostroff.**

Soltara NDA Review Team: **Craig M. Bertha, Ph.D., Young Moon Choi, Ph.D., Emmanuel O. Fadiran, Ph.D., James R. Gebert, Ph.D., Robert J. Meyer, M.D., Guiragos K. Poochikian, Ph.D., Curtis J. Rosebraugh, M.D., M.P.H., Lawrence F. Sancilio, Ph.D.** PHS Unit Commendation: **CAPT Mary E. Purucker, CAPT Ching-Long J. Sun** and **LCDR Craig Ostroff.**

Time Reporting System Development Team: **Sheila K. Andrew, George D. Clanton, Charlene Do, Richard J. Johnson, Marta L. Locklear, Weizhen Lu, Cheryl J. Marshall, Paul J. McCarthy, Stacey L. Nichols, Colleen F. Ratliffe, Timothy L. Rigg, Scott M. Shippey, Linda A. Sigg** and **Binh C. Ta.**

Two Chemistry Review Teams co-located with the Division of Neuropharmacological Drug products: **Thomas A. Broadbent, Ph.D., Danae D. Christodoulou, Ph.D., Gurpreet K. Gill-Sangha, Ph.D., Maria E. Guzewska, Ph.D., Martha R. Heimann, Ph.D., Christy S. John, Ph.D., Donald N. Klein, Ph.D., Richard T. Lostritto, Ph.D., Sherita D. McLamore, Ph.D., Thomas F. Oliver, Ph.D., Hasmukh B. Patel, Ph.D., Lorenzo Rocca, Ph.D., Waclaw J. Rzeszotarski, Ph.D., Robert Seevers, Ph.D.,** and **Mona R. Zarifa, Ph.D.**

Jackie Barber is CDER's incentive awards officer.

Science Day examines issues surrounding dose recommendations

(Continued from page 10)

ommended is indeed the best dose.

He believes that the dosage and administration section of labeling as currently written is "too wordy" considering that a physician spends less than 22 seconds with any given patient's prescription. He prefers very brief, focused information regarding dosing, for example, by bulletining this information.

He is a proponent of separating out major drug-drug interaction information from "minor" ones by highlighting the former in a prominent section of labeling up front, similar to the highlights in the proposed labeling rule.

Another view he espouses is that the Agency should require sponsors to provide exposure-response information in their submissions, justify dose selection more and, further, define the lowest effective dose. Introducing a mechanism for adding Phase IV data and highlighting all new warnings into the labeling of an approved drug were some of his other suggestions.

Robert Temple, M.D., director of the Office of Medical Policy, presented the FDA counterpoint by mentioning that the ICH E-4 document, *Dose-Response Information to Support Drug Registration,* does outline that both the shape and location of the exposure-response curve are important. Furthermore, selection of doses is based on dose response together with judgment about the relative importance of desirable and undesirable effects.

The labeling of many drugs frequently mentions use of the lowest effective dose as the possible starting dose. He acknowledged that problems do exist in life-threatening illnesses where we have been led to use higher doses because of the nature of absence of response. Dose response, in his view, is the most important aspect after safety and efficacy. The E-4 guidance is at http://www.fda.gov/cder/guidance/iche4.pdf.

Study on postmarketing dose changes

James Cross, M.S., a consumer safety officer in the Division of Metabolic and Endocrine Drug Products, presented the results of research on postmarketing dosage changes in drug labels, which he conducted while he was at Georgetown University's Center for Drug Development Science.

He and his coauthors evaluated postmarketing changes in drug dose recommendations for the initially approved indications in 354 of the 499 new molecular entities approved between 1980 and 1999. They found that dosages for one in five of the NMEs changed and that four in five changes were safety reductions.

The median time to change following approval fell from 6.5 years at the beginning of the study period (1980-1984) to 2.0 years (1995-1999). The researchers found that the 1995-1999 NMEs were 3.15 times more likely to change in comparison to the 1980-1984 NMEs.

The authors said reasons for the increased changes include a decrease in foreign marketing experience prior to U.S. approval and the common industry practice of evaluating drugs in Phase III at or near the maximum-tolerated doses established in Phase 1. Their work was published in *Pharmacoepidemiology and Drug Safety* (2002; 11:439-446).

OCPB presentations

The podium presentations included research results from individuals who presented on:

- The microbiological and clinical efficacy of fluoroquinolones in patients with infections.
- Utilization of exposure-response knowledge in regulatory decision-making.
- Simulation characteristics of a new formulation for an oncology agent.
- Survey of transdermal NDAs.
- Review of calcium channel blockers and their interaction with ketoconazole and grape fruit juice.
- Genetic polymorphism of PgP versus exposure of PgP substrates.

The podium session was followed by a formal three-minute presentation made by the principal author of each poster. Posters covered a wide variety of issues such as:

- Evaluating the clinical effectiveness of analgesics, optimal dose selection for pediatric patients.
- *In vitro-in vivo* correlations of parenterals.
- Demographic considerations in bioequivalence studies.
- Assessment of bioequivalence in fed studies.
- Issues related to renal and hepatic insufficiency.
- In vitro evaluation of relative inhibitory potency of macrolides to PgP.
- Dermal microdialysis as a regulatory tool for topicals.
- Understanding schedule dependence of aromatase inhibitor via simulations.
- Comparing various heart rate correction formulas for QT.
- Dosage regimen adjustments based on exposure-response relationships.
- Grapefruit interactions and their labeling.
- Population pharmacokinetic perspectives.
- Pediatric exclusivity issues.
- Survey of pharmacogenetic and pharmacogenomic information in INDs and NDAs.

Science team game

The finale of the day was the participation by all attendees in the game, "Science Funstation." Teams involving eight to 10 individuals were randomly formed. The game was conducted like a TV game show; however, the questions were all relevant to clinical pharmacology and biopharmaceutics. It was a very close race to the finish, and fun was had by all while, of course, learning was taking place.

Science Day, which first started in 1996, features scientific podium and poster presentations by FDA staff, a plenary lecture from a distinguished scientific guest speaker in clinical pharmacology and participation by all in the scientific funstation game.

Over the years the event has been attended by clinical pharmacologists from the Uniformed Services University of Health Sciences, CDER's Office of Generic Drugs, CBER, the Center for Drug Development Science at Georgetown and the National Institutes of Health.

Overall, the latest Science Day was another exciting event where everyone left educated and invigorated.

The first six authors are members of OCPB Science Day Committee, and Larry Lesko is office director.

Raczkowski looks forward to new era of risk management

BY PATRICK E. CLARKE

The director of the Office of Drug Safety is enthusiastic about his office's playing a wider role in a new era of risk management at CDER.

"Historically, we've been focused on post-marketing adverse events," said **Victor Raczkowski, M.D.** "Now, we're trying to make risk management an integral part of drug development throughout a product's life cycle.

"This is a very exciting time for our office," he said. The reauthorization of the Prescription Drug User Fee Act will give FDA new responsibilities to monitor the safety of newly approved medicines. Implementing these will be the major focus for the office. Working groups have already been established to develop guidances and manuals of policies and procedures on risk assessment, risk management and pharmacovigilance practices. The user fee agrement mandates that the guidances be complete by September 2004.

Dr. Raczkowski anticipates that over the five years of PDUFA III, his office will grow substantially. He wants to solidify working relationships between his staff and others within CDER.

"ODS is now involved in pre-, peri- and post-approval risk management," he said. "In addition, a major initiative on my part will be to continue to build collaborative relationships with other parts of CDER, the Agency and outside organizations."

Dr. Raczkowski also wants to maintain a strong collaboration between his office and the Centers for Education and Research on Therapeutics. This research program, authorized in 1997 as part of the FDA Modernization Act, is administered by the Agency for Healthcare Research and Quality in consultation with FDA and other HHS agencies. The mission of the CERTs is to conduct research and provide education that will advance the optimal use of drugs, medical devices and biological products.

"We provide a lot of input into the research centers and provide them with questions to evaluate," Dr. Raczkowski said. "We are heavily involved in setting up workshops on risk management issues with CERTs. There have been workshops on risk communication, risk assessment, and benefit assessment in the past year. We are helping to coordinate workshops on risk communication and the media and on risk management this year. We help to frame research questions."

Dr. Raczkowski wants to see cooperative agreements with external organizations continue. These agreements are with investigators with pharmacoepidemiologic databases that are used to answer questions of scientific and regulatory interest about specific drug exposures and specific adverse events and to estimate risk.

"We're a growing organization with a highly talented and dedicated staff, but we need to coordinate and align our missions and goals with the Center and FDA during this time of growth," Dr. Raczkowski said. "Rather than piling on more commitments to what we already have, I want to think strategically where the Office needs to be in five years and do things in a coordinated and distributed way."

To get there, Dr. Raczkowski said he will use a team-building, facilitative management style that emphasizes people's strengths. "I like problem-solving—taking ambiguous situations and giving them clarity through analytical thinking and interaction with colleagues," he said. "I have a listening and open-minded style. I'm comfortable with delegating to the appropriate level."

A pediatric cardiologist who also holds a master's degree in pharmacology, Dr. Raczkowski started at CDER in 1990 as a medical reviewer CDER's Division of Cardio-Renal Drug Products. He held positions of increasing responsibility in CDER and CBER, including serving as the acting director of the Division of Gastrointestinal and Coagulation Drug Products and the deputy director of the Office of Drug Evaluation III immediately before coming to ODS.

"I've had a long-standing interest in the biological effects of drugs, drug development and drug safety and efficacy issues," Dr. Raczkowski said. He combines his intellectual interest with hands-on experience in the application of risk-management techniques. He has broad Agency experience including his involvement in the risk management of alosetron. This treatment for irritable bowel syndrome was first marketed in February 2000, withdrawn from market for safety reasons in November of the same year and reintroduced in 2002 with a risk management plan.

Among his other achievements, Dr. Raczkowski was the primary clinical author of the draft guidance for industry, *Developing Medical Imaging Drugs and Biological Products.*

He has been the FDA spokesperson on selected drug issues. He is the co-founder of two courses for the Division of Training and Development—one dealing with the design and analysis of therapeutic clinical trials and the other on considerations in the development of diagnostic drugs.

Dr. Raczkowski also sits on the Council for International Organizations of Medical Science VI Working Group, which was established to address issues related to the surveillance and assessment of drug safety data from clinical trials.

Patrick Clarke is a public affairs specialist in OTCOM's Division of Public Affairs.

Process analytical technologies Web site launched

FDA's effort to facilitate the introduction of new technologies to the manufacturing sector of the pharmaceutical industry now has its own Web page on the CDER Internet site at http://www.fda.gov/cder/OPS/PAT.htm.

The process analytical technologies site contains:

- Links to *Pike* articles.
- Presentations from FDA and industry experts.
- Meeting information.
- Educational activities.
- Steering committee membership.
- FDA organization to support the initiative.
- An e-mail link to send questions or comments regarding the initiative.

FDA, SAMHSA join to educate public on dangers of Rx drug abuse

By Ayse Hisim

FDA and the Substance Abuse and Mental Health Services Administration held a press conference on Jan. 16 to launch public education efforts to inform the public of the dangers of misuse of prescription medications and announce new data on prescription medication abuse.

Americans are abusing prescription medications, including opioids, depressants and stimulants, at an alarming rate.

In 2000 there were 697,000 new users of stimulants for non medical purposes, up from 219,000 new users in 1991. For prescription pain relievers, the number of new users reached 2 million in 2000, up from 400,000 during the mid-1980s.

"The public needs to know that just because a medication is safe and even life-saving when used appropriately, it is not harmless if used inappropriately," said SAMHSA Administrator **Charles Curie.** "Abuse of prescription drugs can lead to addiction, misdiagnosis of serious illness, life threatening circumstances and even death."

"FDA recognizes the very real issue of prescription drug abuse," said FDA Commissioner **Mark McClellan, M.D., Ph.D.** "Our job is to strike a balance - to maximize the potential benefits that patients get from these drugs—while minimizing their risks."

Data from the *2001 National Household Survey on Drug Abuse* showed that about 15 percent of 18- and 19-year-olds used prescription medications non-medically in the past year. For persons 12 to 17, 7.9 percent reported past year non-medical use of prescription medications. Among those 18 to 25, 12.1 percent used prescription medications non-medically.

The figures for non-medical use by drug class include:

- 6.4 percent of 12- to 17-year-olds and 9.6 percent of 18- to 25-year-olds having used prescription pain relievers.
- 2.2 percent of 12- to 17-year-olds and 3.4 percent of those 18 to 25 having used stimulants
- 1.7 percent of 12- to 17-year-olds and 4.2 percent of 18- to 25-year-olds having used tranquilizers.

"Young adults, even teens, are taking opioids, anti-depressants and stimulants for recreation," said **H. Westley Clark, M.D., J.D., M.P.H.,** director of SAMHSA's Center for Substance Abuse Treatment. "They do not seem to realize that this misuse can lead to serious problems with addiction."

One class of prescription drugs, pain relievers, is of particular concern to both CDER and CSAT. "When used correctly and under a doctor's supervision, the benefits of prescription pain relievers outweigh their risks," said **John Jenkins, M. D.,** director of CDER's Office of New Drugs. "But abuse them, or mix them with illegal drugs or alcohol, and you can wind up dead. Even using them with other prescription drugs can lead, in some cases, to life-threatening problems."

An additional report released by SAMHSA from its Drug Abuse Warning Network shows that visits to emergency departments in hospitals increased significantly from 1994 to 2001 for narcotic prescription pain relievers.

Visits naming oxycodone increased 352 percent; methadone 230 percent; morphine 210 percent; and hydrocodone 131 percent. The data show that persons showing up for emergency treatment often used more than one drug.

CDER and CSAT have joined to launch a public education effort focused on prescription medications. Nearly 100 print and broadcast media outlets made use of the story and materials distributed at the news conference.

The first products of this cooperative endeavor feature posters, brochures and print advertisements.

Materials include two print public service announcements—*The Buzz Takes Your Breath Away* and *It's to Die For*—and a consumer education brochure, *The Buzz Takes Your Breath Away—Permanently.*

The educational materials are targeted to 14- to 25-year-olds, but they are relevant for all consumers who use prescription pain relievers non-medically.

These are available on CDER's Web site at http://www.fda.gov/cder/consumerinfo/DPAdefault.htm. To obtain any of the graphic images for printing, please call 301-827-1243 or 888-INFO-FDA. You can also e-mail your request to: dpapubs@cder.fda.gov.

FDA consumer information on the dangers of abusing prescription pain relievers is available by calling 1-888-INFO-FDA. SAMHSA's reports and other information are available at http://www.samhsa.gov.

Ayse Hisim is a public affairs specialist in OTCOM.

FDA publishes final rule to require labeling about antibiotic resistance

FDA announced a final rule outlining new labeling regulations designed to help reduce the development of drug-resistant bacterial strains. This final rule is aimed at reducing the inappropriate prescription of antibiotics to children and adults for common ailments such as ear infections and chronic coughs.

The new rule applies to all systemically absorbed human antibacterial drugs and requires statements in several places in the physician labeling advising that these drugs should be used only to treat infections that are believed to be caused by bacteria. The rule also requires a statement in the labeling encouraging physicians to counsel their patients about the proper use of these drugs and the importance of taking them exactly as directed. This is part of ongoing efforts at FDA to encourage the development of new antimicrobials while preserving the usefulness of already existing ones.

"Antibacterial resistance is a serious and growing public health problem in the United States and worldwide," said FDA Commissioner **Mark McClellan, M.D., Ph.D.**

An electronic version of the final rule can be found at http://www.fda.gov/OHRMS/DOCKETS/98fr/00n-1463-nfr00001.pdf.

More information about antibiotic resistance can also be found on FDA's Web site at http://www.fda.gov/oc/opacom/hottopics/anti_resist.html.

FDA initiative aims at reducing time, costs of product development

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Agencywide working group drawn from the four medical product review centers (drugs, biologics, devices and veterinary medicine). The group included the center directors and their respective directors of new product review.

Their full report is at: http://www.fda.gov/bbs/topics/NEWS/2003/beyond2002/report.html.

Their executive summary is at: http://www.fda.gov/bbs/topics/NEWS/2003/beyond2002/execsumm.html.

Calendar year 2002 performance

The report also summarizes product review performance during 2002. For example, CDER's drug approval statistics last year reflect a decline in the number of submissions during the past few years. In calendar year 2002, the types of applications, the number approved and the median total approval times were:

- Priority new drug applications: 11 in 19.1 months.
- Priority new molecular entities (a subset of NDAs): seven in 16.3 months.
- Priority efficacy supplements (for new or expanded uses of an already approved drug): 19 in 6.0 months.
- Standard NDAs: 67 in 15.3 months.
- Standard NMEs: 10 in 15.9 months.
- Standard efficacy supplements: 133 in 10.0 months.
- Generic drug applications: 384 in 18.3 months.

Last year saw a steep rise in median total approval times for priority NDAs and priority NMEs compared to calendar year 2001 when the median approval times for both were 6.0 months. This was a statistical artifact caused by a tail of submissions from calendar year 2000 that was larger than the cohort submitted and approved in 2002. For example, there were three priority NME applications submitted in and approved in 2002. These three had a median approval time of 5.8 months, so there is no evidence that our current review performance for priority applications is lagging. (A CDER guide to understanding median approval time statistics is available at http://www.fda.gov/cder/present/MedianAPtime/index.htm.

Avoiding multiple review cycles

To address the problem of marketing delays and increasing product development and review costs, the Agency will begin by analyzing the root causes of product approvals that require more than one review cycle. Potential remedies for preventable cases of multiple-cycle review include improving the quality and frequency of communications between FDA and sponsors of drugs and implementing a continuous marketing application pilot project.

Rather than a change of standards or a reduction in review time, these efforts to reduce approval times and costs are geared to building excellence and predictability into the product development process so that the required scientific data are present in the marketing application the first time it is submitted.

Because a review cycle takes time—typically six months for a priority new drug application and 10 months for a standard new drug application—and because many products that are ultimately successful are not approved on the first cycle, avoiding multiple cycles where possible can lead to substantial improvements in product availability and cost.

To help understand the reasons for multiple-cycle reviews, CDER undertook a retrospective study of the causes for approval delays for standard and priority new molecular entities.

Standard NMEs studied were those with total approval times greater than 12 months in 2000 and 2001. Fifty-seven percent of these applications had times greater than 12 months, ranging from 12.1 to 54.4 months. The most frequent primary reasons for delay on the first cycle were safety issues (38 percent) followed by efficacy issues (21 percent), manufacturing facility issues (14 percent), labeling issues (14 percent), chemistry, manufacturing, and controls issues (10 percent), and submission quality (3 percent).

Priority NMEs were those with total approval times greater than 6 months in 2000 and the first eight months of 2001. Fifty-two percent of these applications had total approval times greater than six months, ranging from 6.6 to 54.4 months. The most frequent primary reasons for delay in approval on the first cycle were chemistry, manufacturing, and controls issues (46 percent) followed by safety issues (27 percent), efficacy issues (18 percent), and manufacturing facilities issues (9 percent).

Implementing quality systems

FDA will establish a continuous improvement/quality systems approach to medical product reviews across the agency. This will include enhanced reviewer training on good review practices, institution of peer review within the FDA review process and further development of standards for the review process.

Clearer guidance

To achieve the third broad objective, FDA will support the development of new technologies by creating clearer guidance for product approvals in priority areas.

The initial focus for guidances will be on diseases most in need of improved therapies, including cancer, diabetes and obesity. FDA will develop these in a collaborative manner, working with external experts and interest groups. The Agency expects that many of the guidances will also involve collaboration among several centers.

Emerging technologies

FDA believes we can help speed potentially important emerging technologies to the market by reducing regulatory uncertainty and increasing the predictability of product development. FDA will clarify the regulatory pathways in three emerging areas of technology: cell and gene therapy, pharmacogenomics and novel drug delivery systems.

FDA Science Forum to be held April 24-25 in D.C.

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A poster session featuring all areas of FDA regulatory science will be presented to provide an opportunity for interested scientists to engage in information exchange with our scientists. Additionally, this forum hosts its first full exposition of scientific products and technologies.

While on-site registration will be available, seating will be limited. So register soon. The registration fee is $25.

For more information on primary scientific topics and speakers, please visit: http://www.dcscienceforum.org.