news along the pike

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CENTER FOR DRUG EVALUATION AND RESEARCH

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INSIDE . . .

Center nurses work to improve patient safety

Everyday jobs at CDER promote safe use of approved drugs

BY VIRGINIA GIROUX, C-FNP, MSN, AND E. JANE MCCARTHY, CRNA, PH.D., FAAN

While revitalizing the CDER Nurses Network recently (page 10), we realized that nurses are playing an important role in the Center related to patient safety and drugs.

With all the negative news about CDER's role in patient safety, we wanted to share some of our nurses' responses to our request to comment on their role in ensuring the public health through the safe use of drugs.

"I have been working with post-marketing safety surveillance at FDA for nine years," said **Carol Krueger, R.N.,** a consumer safety officer on the Adverse Drug Event Reporting Compliance Team in the Office of Compliance's Division of Compliance Risk Management and Surveillance. "The ADE Team oversees field inspections of post-marketing adverse drug event reporting, working to ensure that the Office of Drug Safety and Office of New Drugs receive post-marketing safety information. We are actively involved in the Center's review and monitoring of risk management programs for approved drug products."

Holly Wieland, R.N., MPH, in the Division of Metabolic and Endocrine Drug Products, does labeling reviews for new drugs and for supplemental applications to previously approved drug products. "The labeling has to be compliant with the recommendations of the review team and has to be written and graphed in such a format as to be easy to read and understand," she said.

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CDER's Commissioned Corps aids hurricane victims

BY PATRICK E. CLARKE

The catastrophic destruction caused by four hurricanes in a five-week period led the U.S. Public Health Service Commissioned Corps to deploy more than 500 officers to help the residents of Florida and Alabama, according to **RADM John Babb,** the director of the PHS Office of Force Readiness and Deployment.

CDER sent a number of officers, including **LCDR Catherine Yu,** senior health promotion officer in OTCOM's Division of Drug Information. Her two-week deployment started at the special needs shelter in Orlando but ended in Pensacola where Hurricane Ivan caused extensive damage. "I was part of a smaller team sent to assist Sacred Heart Hospital meet its operational needs in providing care to the Pensacola community," Yu said.

Many of the regular hospital staff couldn't make it to work, needed time to fix and clean

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Oncology, non-Rx offices highlight OND reorganization

BY JOHN JENKINS, M.D., AND SANDRA KWEDER, M.D.

The Office of New Drugs will be reorganized when we move to White Oak next spring. This will better balance our workload and resources, improve collaboration through better grouping of clinical indications and complete the integration of biologic therapeutics.

Our new OND will consist of six subordinate offices, 15 review divisions and an immediate office.

We will look like this:

Office of Oncology Products
- Division of Drug Oncology Products
- Division of Biologic Oncology Products
- Division of Medical Imaging and Hematology Products

Office of Drug Evaluation I
- Division of Cardiovascular and Renal Products
- Division of Neurology Products
- Division of Psychiatry Products

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JOE'S NOTEBOOK

HHS, FDA, CDER strategic goals

The Center's strategic initiatives feed into the strategic goals for the year ahead announced by the Department and the Agency. Four of eight HHS goals relate directly to the work we do: They are:

- Enhance the ability of the nation's health care system to effectively respond to bioterrorism and other public health challenges. This goal includes both response to attacks and steps to improve the safety of food and medical products.
- Enhance the capacity and productivity of the nation's health science research enterprise. This HHS goal specifically identifies accelerated development of new drugs and biological products.
- Improve the quality of health care services. This goal includes both reducing medication errors and promoting the development and use of an electronic health information network.
- Achieve excellence in management practices.

You can find more on the HHS goals at http://aspe.hhs.gov/hhsplan.

FDA

FDA in a recent publication, *Progress and Priorities 2004: Protecting and Advancing America's Health,* provided an update on its strategic plan announced in 2003. The report focused on accomplishments and high priorities for the coming year in six areas:

- Enabling technology development and innovation.
- Patient and consumer protection.
- Protecting the homeland—counterterrorism.
- Using risk-based management practices.
- Empowering consumers for better health.
- Improving FDA's business practices.

You can find the report at http://www.fda.gov/oc/initiatives/reports/priorities2004.html. (I have some printed copies of the FDA report. If you'd like one for your reference, send me an e-mail.)

CDER

Our Center's strategic direction, as always, remains focused on articulating and enforcing our mission to ensure that Americans' medicines are safe, effective and available. A second overarching objective is to implement quality systems within CDER. This involves among things assessing the Center's current quality systems or similar activities.

The Center has 10 supporting strategic initiatives:

- Recruit and retain world-class staff.
- Establish and enforce management expectations and accountability.
- Develop specific training modules for performing review activities or on regulatory procedures and policies.
- Develop peer and expert assistance capability to support business processes. This includes developing peer and expert assistance capability for support during application review.
- Eliminate unnecessary multiple cycle reviews without compromising standards. This includes both new and generic drug review.
- Develop a process for systematic review of safety data after approval.
- Develop an integrated approach to regulation of drug quality.
- Review the current policy and guidance process.
- Evaluate and improve administrative support procedures.
- Implement enterprise architecture.

The Center's strategic initiatives were presented by **Stephen Galson, M.D.,** in the State of the Center address. Both the slides and the multimedia video presentation are available on the CDERnet to FDA employees at http://cdernet.cder.fda.gov/dtd/SEMINARS/Fall04/fall04.htm.

news along the pike

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

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

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cGMP final report: FDA forms Council on Pharmaceutical Quality

Following the second anniversary of the launch of the Pharmaceutical Manufacturing Initiative, FDA issued a final report, which discusses:

- The Agency's completed assessment of the current good manufacturing practice regulations, current practices and the new tools in manufacturing science that will enable a progression to controls based on quality systems and risk management.
- Specific steps the Agency has taken and will take to develop and implement quality systems management and a risk-based product quality regulatory system.

Some of the actions FDA is taking as it moves from analysis to implementation include:

- Creating a Council on Pharmaceutical Quality within FDA. The council will develop policy and manage change.
- Establishing a new risk-based pharmaceutical quality assessment system to replace the current chemistry, manufacturing and controls review system in the Office of New Drug Chemistry.
- Issuing a draft guidance on the role of quality systems. This will ensure our regulatory practices encourage progress in the pharmaceutical industry as well as enable manufacturers to tailor their quality system to fit their specific manufacturing environment.
- Taking more systematic risk-based approaches to inspectional oversight of pharmaceutical manufacturing. This will start with a pilot implementation of a risk-based model for prioritizing cGMP inspections for domestic manufacturing sites.
- Issuing a final guidance on aseptic processing used in the manufacturing of sterile drugs. This will encourage the adoption of modern science and technology and risk-based approaches.
- Issuing a final guidance on process analytical technology. This framework will allow regulatory processes to adopt state-of-the-art technological advances in drug development, production and quality.
- Publishing a draft guidance on good manufacturing practice for combination products.
- Continuing active international collaboration in pharmaceuticals and veterinary medicines. This will lead to the implementation of an internationally harmonized plan for a pharmaceutical quality system based on an integrated approach to risk management and science.
- Seeking membership in the Pharmaceutical Inspection Cooperation Scheme. This is a cooperative agreement among national health regulatory authorities. Among the groups's aims are leading international development, implementation and maintenance of harmonized cGMP standards and quality systems for pharmaceutical inspectorates.

In addition, the following underscore the agency's commitment to realizing the specific goals of this initiative:

- A proposed rule amending Part 11, Electronic Records, Electronic Signatures – Scope and Application is expected to be published for public comment in 2005.
- A draft guidance on the use of computerized systems in clinical trials, once finalized, will replace the guidance of the same name issued in April 1999.
- The implementation of a technical dispute resolution process for cGMP disputes.
- The upcoming finalization of guidance on preparation and use of a comparability protocol for assessing chemistry, manufacturing and control changes to chemical entities, protein drug products and biological products.
- Improved integration of the preapproval and cGMP inspection programs through training, certification and Center detail opportunities for the 26 candidates chosen for the Pharmaceutical Inspectorate. They have just completed their first level of training.
- The implementation of a revised charter by the Team Biologics Operations Group that adopts a quality systems management framework, improves processes for communication and coordination between headquarters and the district offices and further integrates product specialists into the program.

More information, as well as the final report, is available at http://www.fda.gov/cder/gmp/.

CDER employees step lively in Office of Women's Health Fitness Challenge

By Patrick E. Clarke

The 1,024 FDA employees who walked a total of 725,571,119 steps in the 100-day-long Office of Women's Health Fitness Challenge are all winners just for participating, according to **Deborah Kallgren,** the OWH challenge coordinator.

Of course, any contest has actual winners, too, and CDER employees stepped lively to grand prize victories in several categories:

- **Aloka G. Chakravarty**, from the Office of Biostatistics, was the Individual Most Improved over Baseline in the 4K Step Category with 862,003 steps.
- The Team with the Highest Average Steps in Category in the 4K Step Category was "The Fitness Enforcers," consisting of **Shawnte Adams, Lavonia Huff, Betty Jones** and **Jocelyn Lewis,** from the Office of Compliance, and **Sandra Whetstone,** from FDA's Office of Regulatory Affairs.
- The Highest Percent of Team Members Meeting Overall and Daily Goals in the 4k Step Category was the "CDER 570 4K Steppers," consisting of **Gary Bond, Carol Hill, Ladan Jafari** and **Larry Sancilio,** all from the Division of Pulmonary Drug Products in the Office of New Drugs.

All grand prize winners were treated to a lunch with Acting FDA Commissioner **Lester Crawford, DVM, Ph.D.**

"And it was healthy food, too, and no desserts," Lewis said. "Remembering to put the pedometer on and then remembering to record it after you did your steps was the hardest thing." Not only did she lose some weight from completing the challenge, but she also feels fit. "It helped that I have a dog that needed to be

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Retreat focuses on animal models for biologicals, nanoparticles

BY GARY P. BOND, PH.D., DABT

At the pharm/tox semi-annual scientific retreat held Sept. 29, CDER reviewers focused on:

- Species selection for toxicology studies of biotechnology drugs.
- The effects of nanoparticles on respiratory health.
- Carcinogenicity assessments and regulatory recommendations for the antidiabetes agents known as peroxisome proliferator-activated receptor agonists or PPARs.

The retreat started with welcoming remarks from **Hanan Ghantous, Ph.D., DABT,** the chairperson of the meeting. The program contained a full slate of timely and relevant information from expert speakers.

Species selection for biologicals

Species selection for toxicology studies conducted with biotechnology-derived products. **Andrea Weir, Ph.D., DABT,** from the Division of Therapeutic Biological Internal Medicine Products, discussed a number of biological products transferred from CBER to CDER in October 2003. These include monoclonal antibodies for *in vivo* use, cytokines, enzymes, growth factors, thrombolytics and extracted proteins.

Differences between these products and small molecules have resulted in different testing strategies for these two groups of products. In order to yield scientifically meaningful results, toxicology studies for biological products need to be conducted in pharmacologically relevant models. These are species that possess the epitope or receptor for the product. An epitope is the specific part of a molecule to which an antibody binds.

Toxicology studies in non-relevant models may be misleading and are discouraged. Multiple approaches can be used to define the relevant model. These include, but are not limited to: functional pharmacology studies, flow cytometry to assess binding, and/or immunohistochemistry.

If no relevant model can be identified, alternate approaches can be used, such as surrogate proteins, transgenic animals, or animal models of disease. The toxicology testing strategy for biological products is supported by a number of guidance documents. The primary document is International Conference on Harmonization's ICH S-6, *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (http://www.fda.gov/cder/guidance/1859fnl.pdf).

Cardiac biomarkers

ILSI troponin effort. **Elizabeth Hausner DVM, DABT, DABVT,** Division of Cardio-Renal Drug Products, presented an update from the troponins working group of the Health and Environmental Sciences Institute of the International Life Sciences Institute. The institute is a non-profit scientific organization that advances the state of science related to human health, toxicology, risk assessment and the environment.

Troponins are very specific and sensitive markers for cardiac muscle cell death. The ILSI working group has divided its proposed studies of troponins into "analytical " and "biological" validation. The ongoing analytical validation studies seek to compare the commercially available troponin assays side by side and determine which assay is appropriate for use in which of the commonly used laboratory animal species. This critical phase is being conducted by Fred Apple, Ph.D., from the University of Minnesota School of Medicine.

The results are of particular importance because recently published studies using human samples showed that all the commercially available troponin assays had a coefficient of variance exceeding the goal of 10 percent at the decision-making point. The coefficient of variance is a statistical measure of a test's variability.

The "biological" phase, planned for next year, will study mechanical and pharmacological cardiac damage.

ICH draft QT guidance

ICH S-7B guidance (step 2 revision): The Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals. **John Koerner, Ph.D.,** Division of Cardio-Renal Drug Products, discussed this draft guidance, which describes a non-clinical testing strategy for assessing the potential of a test substance to delay ventricular repolarization. Dr. Koerner noted that this guidance incorporates a uniform integrated risk assessment that includes potency relative to reference agents, *in vivo* safety margin, assay sensitivity and specificity, dose limiting toxicities, contribution of metabolites and other factors. The ICH expert working group next meets in May and will discuss comments received and address predictability of non-clinical assays. The draft is at http://www.fda.gov/cder/guidance/5533dft.htm.

Nanoparticles

Impact of nanoparticulates on respiratory health: Studies in rats and relevance of findings for humans. **Dave Warheit, Ph.D., DABT,** DuPont Haskell Laboratory, reported on a study to evaluate the toxicity of intratracheally instilled single-wall carbon nanotubes in the lungs of rats. The pulmonary toxicity of intratracheally instilled carbon nanotubes was compared to a positive control particle-type, quartz, carbonyl iron particles (negative control particle-type), and to phosphate-buffered saline (negative control). After exposures, the lungs of test and control rats were assessed both using bronchoalveolar lavage, fluid biomarkers, cell proliferation methods and by histopathological evaluation of lung tissue at 24 hours, one week, one month and three months post-instillation.

High dose exposures to the nanotubes produced mortality in about 15 percent of the rats within 24 hrs post-instillation. This mortality was due to mechanical blockage of the large airways by the instillate and did not result from inherent lung toxicity of the instilled nanotube particulate.

Data from the bronchoalveolar lavage and cell proliferation studies demonstrated that lung exposures to quartz particles produced persistent enhancement in pulmonary inflammation, cytotoxicity and

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Pharm/Tox retreat examines rodent carcinogenicity in drug class

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pulmonary inflammation, cytotoxicity and lung cell parenchymal cell proliferation indices. Alternatively, single-wall carbon nanotube exposures produced transient inflammatory and cell injury effects at one day postexposure, due primarily to the blockage of airways and resulting injury by the instillate.

Lung exposures to the nanotubes in rats produced a non-dose-dependent foreign tissue body reaction, as evidenced by a series of multifocal mononuclear granulomas. Surprisingly, the bronchoalveolar lavage and cell proliferation results were not predictive biomarkers of the nanotube-induced granulomatous lesions, unlike pulmonary responses to quartz particles. The observation of a nanotube dust-induced foreign tissue reaction is not consistent with:

- The lack of lung toxicity by assessing lavage parameters.
- The lack of lung toxicity by measuring cell proliferation parameters.
- An apparent lack of a dose-response relationship.
- Non-uniform distribution of lesions.
- The paradigm of dust-related lung toxicity effects.
- Possible regression of effects over time.

Physiological relevance of these findings and reconciliation of apparent discrepancies in this lung bioassay study remain to be determined.

PPAR agonist carcinogenicity

Carcinogenicity assessments for the peroxisome proliferator-activated receptor agonists: Tumor findings and regulatory recommendations. **Jeri El-Hage, Ph.D.,** a pharmacology supervisor in the Division of Metabolic and Endocrine Drug Products, discussed the available data from 11 sets of rodent carcinogenicity studies (two-year studies in mice and rats) that have been completed for 11 PPAR agonists. PPAR agonists are being investigated for several conditions including diabetes and high cholesterol.

The results of the carcinogenicity studies demonstrate that PPAR agonists are multi-species, multi-strain, mulitsex and multi-site carcinogens in rodents. The tumor types commonly observed include hemangiosarcomas in mice, transitional cell carcinomas of the urinary tract in rats, lipoma/liposarcomas in both species and sarcomatous tumors at multiple sites, such as kidney, stomach, uterus and skin.

The mode of action for the development of these tumors remains to be determined. However, because the tumors are located at sites known to have high concentrations of PPAR receptors and tumor-induction potency appears to be correlated with PPAR receptor activation potency, a receptor-mediated mechanism and human relevance cannot be ruled out.

Currently, rodent carcinogenicity study results must be submitted for Agency review prior to the conduct of clinical studies lasting longer than six months. More detailed information regarding this topic is available on the CDER Web site (www.fda.gov/cder/present/DIA2004) or, for FDA employees only, on the CDERnet pharmacology/toxicology site (http://cdernet.cder.fda.gov/pharmtox/pharmtox.htm).

Investigative approaches to understanding the mode of action for PPAR-induced rodent tumors: Bladder carcinomas in rats and hemangiosarcomas in mice. Richard Storer, Ph.D., from Merck Research Laboratories, discussed investigational strategies to understand mode of action for rodent tumor findings in two-year carcinogenicity studies with PPARγ and PPARαγ dual agonists developed for treatment of type II diabetes.

Building upon earlier presentations at a workshop organized by CDER's Dr. El Hage at the 2004 DIA meeting in Washington in June, Dr. Storer reviewed the data for urinary bladder tumor induction in rats and hemangiosarcoma induction in mice with PPAR agonists. With respect to the mode of action for rat bladder tumorigenesis, Dr. Storer cited the extensive body of literature showing associations between treatment-related changes in urine composition which promote microcrystalluria and calculi and the induction of proliferative lesions in transitional urothelium, particularly in bladders of male rats.

He then reviewed the marked changes seen in urine pH, monovalent (Na+, K+) and divalent cation (Ca++) concentrations and urine crystals in the second year of the rat carcinogenicity study with Merck's PPARαγ dual agonist. These changes were associated with bladder neoplasms localized predominantly to the ventral cup of the bladder where precipitates settle by gravity.

Dr. Storer suggested that further investigational studies of the mode of action for this effect should focus on the manner in which PPAR agonists produce these marked changes in urine composition, enhance formation of microcrystalline precipitates that are locally cytotoxic to the urothelium and ultimately promote bladder neoplasms.

With respect to hemangiosarcomas in mice, Dr. Storer reviewed the published literature on previous investigative studies of troglitazone's mode of action in producing this effect. Noting the focus has been on PPARγ-mediated effects in adipose tissue, Dr. Storer discussed the hypothesis that PPARγ agonism leads to changes in local concentrations of endogenous angiogenic factors promoting the neovascularization required for expansion of adipose tissue depots.

He then suggested that chronic stimulation of cell proliferation of endothelial cells results in either an enhanced mutation frequency and rate of spontaneous transformation or promotion of preexisting spontaneous transformants that are the source of the historical background incidence of this tumor in control mice.

Dr. Storer concluded by advancing a hypothesis that endogenous retroviral sequences in mice may play a role as insertional mutagens with the potential to immortalize endothelial cells by activating the expression of growth factor genes. He suggested that exploration of this hypothesis could be key to understanding the apparent species specificity of this lesion for mice.

PARαγ dual agonist. **Fred Alavi, Ph.D.,** Division of Metabolic and Endocrine Drug Products, dis-

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Theme: Current environment for new drug research, development

BY RAY BAWEJA, PH.D., SOPHIA ABRAHAM, PH.D., SANDRA SAUREZ, PH.D., ABIMBOLA ADEBOWALE, PH.D., CHARLES BONAPACE, PHARM.D., SRIKANTH NALLANI, PH.D., PATRICK NWAKAMA, PHARM.D., VENKAT JARUGULA, PH.D., SHIEW MEI HUANG, PH.D., AND LARRY LESKO, PH.D.

The 13th Annual Science Day sponsored by the Office of Clinical Pharmacology and Biopharmaceutics was held in October. This occasion celebrated the theme of "The Current Environment for Pharmaceutical Innovation: The Challenges of New Drug R&D."

Both **Janet Woodcock, M.D.,** FDA's acting deputy commissioner, and **Steven Galson, M.D.,** CDER's acting director, were able to join us for this Science Day. In her opening remarks, Dr. Woodcock spoke about new and on-going initiatives in the Center. To set the theme for the day and to provide a prelude for the guest speaker's presentation, she mentioned that she is a strong supporter of efficient drug development but acknowledged that even today this process is quite empirical.

However, as a result of Center initiative, there has been considerable progress in the cGMPs regarding pharmaceutical quality control and manufacturing operations where critical controls of formulation quality can be assessed and linked to the clinical performance of the drug. She stressed the importance of the Critical Path Initiative and stated that while technology and research have improved by leaps and bounds in the area of pharmaceuticals, it has not been parlayed into improving and streamlining the drug development process.

Dr. Woodcock also spoke on disease-progression modeling, and pharmacogenomics. A new guidance for pharmacogenomics is currently under preparation in the Center and, when issued, should provide great benefit from a scientific and regulatory viewpoint in bringing efficiency to the overall drug development procedure.

Another initiative being considered is an "exploratory IND" where CMC and pharmacology/toxicology would link up for "Phase 0" studies looking into *in vitro* proof of mechanism studies, such as receptor occupancy, and also for simplified procedures to screen compounds.

Kenneth Kaitin, Ph.D., director of the Tufts Center for the Study of Drug Development, delivered the keynote address.

At the outset he mentioned that the current national drug landscape is one of cost containment and productivity. In the latter, for example, R&D costs are rising considerably but there is certainly less return. The "hot button" topics that he focused on included drug prices, affordable access, innovation of new drugs, safety of the drug supply chain, conduct of clinical trials and drug advertising.

The current worldwide focus on containing health care expenditures and the highly competitive pharmaceutical marketplace have brought considerable pressure on pharmaceutical companies to improve their efficiency and productivity in new drug development.

Both the cost and the time to bring a new drug product to market have increased; therefore, many firms are reexamining inefficient models of research and development and embracing new approaches to enhancing productivity and performance. For example, the current thinking for firms is the "blockbuster" mentality of developing only commercially high-dividend drugs rather than a science-driven approach that would yield a successful drug but one that would not be as high-dividend yielding.

Other reasons for cost increases are that, from a medical standpoint, chronic and complex indications are the ones now left to treat; the size of clinical trials has increased; and the still considerable late-stage attrition of drugs under development rather than an early "kill" of the compound.

New technologies are playing a critical role in helping firms limit late-stage surprises and failures and ensure that compounds entering the development pipeline are indeed the ones that will most likely succeed. The new paradigm, therefore, is "kill early, kill often" to ensure that the best compounds go through the pipeline.

Rigorous proof of concept procedures are being implemented before embarking on large-scale clinical trials. Another approach is to apply new technology, such as biomarkers, to gauge the activity and potency levels of compounds before send-

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Pharmacology/toxicology reviewers' retreat

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genicity data for a PPARαγ agonist. The case study discussions were centered on the rodent carcinogenicity data demonstrating tumor findings at all doses including those with drug exposures comparable to therapeutic doses. The implications of the carcinogenicity study results for patient safety in long-term studies and continued product development were discussed.

Parathyroid Hormone rhPTH1-34. **Gemma Kuijpers, Ph.D.,** Division of Metabolic and Endocrine Drug Products, also discussed rat carcinogenicity findings with parathyroid hormone-like drugs that are used to treat osteoporosis based on their respective actions on bone resorption and formation. Of interest were the clinical relevance of the rodent findings and the impact of the findings on Phase 3 trials and the regulatory approval process.

The retreat was organized by pharmacology and toxicology reviewers and staff from various divisions at CDER including **Hanan Ghantous** (chair), **Mamata De, Pat Harlow, Wafa Harrouk, Dave Hawver, Steve Kunder, Shwu-Luan Lee, Yanli Ouyang, Tom Papoian, Herman Rhee, Adele Seifried** and myself.

Gary Bond is a pharmacologist in the Division of Pulmonary and Allergy Drug Products and would like to acknowledge the assistance of speakers and retreat committee members in the preparation of this article.

Keynote speaker Kaitin sees need for improved decision-making

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ing them forward into development. He linked all his industry viewpoints to the past decade of the FDA where the sequential stages of PDUFA, FDAMA and the Critical Path Initiative, have assisted in speeding the availability of new drugs to the American public.

The significant change in R&D strategy and practice needed from now on, he concluded, should include:

- Improved quality of decision-making.
- Better use of available data.
- Maximizing interactions with the Agency.
- Exploiting new tools and technologies.
- Strategic outsourcing.
- Rapid adoption of technological advances.

Presentations

Podium presentations included the following:

- Application of a model-based analysis to improve the drug development plan for a life-threatening disease.
- Critical Path Initiative: Overview and the potential uses of medical imaging in drug discovery.
- Impact of correction formulae on the QTc Interval with a drug suspected to prolong the QT interval: A study gone amiss.
- Population pharmacokinetics for assessing drug-drug interaction: Considerations during regulatory review.
- Impact of sample size and frequency of QT recording on the reliability of thorough QT prolongation assessments.
- Pooled analysis: An alternative design in establishing bioequivalency.

Posters

Poster presentations included the following:

- Pharmacokinetics and pharmacodynamics of intravenous methylene blue in rhesus monkeys.
- Optimizing the dose titration scheme of an anticoagulant drug using simulation.
- A Web-based pharmacometrics learning resource.
- Visual inspection practices to assess the influence of exposure.
- Time course of spinal bone-mineral density change in healthy and osteoporotic, post-menopausal women.
- Model-based longitudinal data analysis can lead to efficient drug development.
- Use of predictive check to qualify covariate models.
- Assessing QT study designs with clinical trial simulation.
- Labeling of drugs that interact with oral contraceptives.
- Evaluating the efficacy study design of an anesthetic.
- Sensitivity of QT studies: Variabilities in baseline QT measurements.
- Placebo as a reference control in QT risk assessment.
- Bioequivalence of highly variable drugs in generic drug applications.
- CPB issues for fixed dose combination and co-packaged drug products for treatment of HIV.
- Chemical substituent contributions to passive drug permeability across artificial membranes.
- A comparison of clinical study designs using fixed dosing versus pharmacokinetic parameter modified dosing.
- NONMEM estimation methods by visualization.
- Clinical trial simulation approach for designing studies investigating the similarity in PK-PD relationships between different patient populations.
- Prospectively individualizing dose regimens in Phase 3 trials of an anti-infective drug.
- Improving pediatric labels through the Pediatric Initiatives.

FDA history presentation

John Swann, Ph.D. from the Office of FDA History presented the history and evolution of the FDA. Beginning with the Pure Food and Drug Act of 1906, through the sulfanilamide and thalidomide incidents of 1938 and 1962 respectively, into the Kefauver-Harris amendments and the current stage with PDUFA and FDAMA, his presentation educated the audience about the history of the Agency.

Background

Science Day which began in 1996 continues to feature both podium and poster presentations and a lecture from a distinguished guest speaker.

This year, the program was expanded and modified to include the talk on FDA history and a lunchtime concert by the U.S. Public Health Service Band.

Over the years the event has seen participation of clinical pharmacologists from the Uniformed Services University, Walter Reed Army Institute of Research, Office of Generic Drugs, CBER, Center for Drug Development Science at Georgetown, Virginia Commonwealth University, and the National Institutes of Health.

To date there have been around 225 scientific presentations which include six podium and 20 posters for this year.

Distinguished guest speakers have shared the latest findings in the field of medicine, clinical pharmacology, optimization of the drug development process, and have included Drs. Curtis Wright, Carl Bjornsson, David Greenblatt, William Jusko, Bill Evans, Janice Schwartz, Jay Cohen, Stephen Naylor and, for this year, Dr. Kaitin.

The main theme of OCPB Science Day all along has been to share and exchange scientific information and ideas among clinical pharmacologists.

The finale of the day was a talent hour. Presentations included a slide presentation of marine life, karate demonstrations of two internationally varying styles, hymnals played on the mouth organ, a well-choreographed group dance, embroidery exhibits and a folk tune ensemble—a very enjoyable and memorable hour.

Overall, this turned out to be another exciting, knowledge-gaining day where everyone at the end of the day came out knowledgeable, well-informed and invigorated.

The authors are all members of CDER's Office of Clinical Pharmacology and Biopharmaceutics. Dr. Lesko is OCPB director.

CDER Commissioned Corps officers help with hurricane relief

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their homes or were just exhausted from working long hours, according to Yu.

"Health concerns arose as a result of the hurricanes. There were chainsaw wounds from people cutting away trees, trauma from falling debris and infections and diarrhea because of contaminated water. Really, there were too many problems to list,"

Yu put in 12-hour days staffing the inpatient, outpatient and pediatric pharmacies. "I think every one of us has a built-in desire to serve those in need, and I was one of those blessed to actually do so," Yu said.

LCDR Krista Scardina, a medical affairs coordinator in the Office of Generic Drugs, was deployed to Tallahassee and was housed with the Florida State Operations Center. "My team acted as liaisons to help state officials obtain assistance from the federal government," Scardina said. "In addition, we helped state officials assess the status of hospitals after the hurricane."

The status of hospitals in the area was often grim, as many of them had no power or water. "That would be a life-threatening problem for dialysis patients—so, we helped state officials identify federal facilities within a 100-mile range of Pensacola that could support the function," Scardina said.

"I had the opportunity to see the direct results in the field, but the relationship of trust we built with the state people was very rewarding," Scardina said.

LT Jeen Min, a regulatory management officer also from OGD, got to see direct results as well. "I worked as a pharmacist out of the special needs center at the Orange County Convention Center," Min said. "Fortunately, the hurricane didn't hit that area, so only about 200 people came to the center."

Because there were so many health care workers there, "we were able to really spend time with patients and meet their needs," Min said.

LT Techara Bouie, a regulatory project manager in the Office of New Drug Chemistry, was also working out of the special needs shelter in Orange County. "I was placed on the discharge planning team. We coordinated the discharge of all special needs patients out of shelters," Bouie said.

Her team did discharge assessments and would contact family, friends, neighbors or even the power company to be certain their patients had some place safe to go. "We successfully discharged 117 patients. That was very satisfying because you could actually see the progress that was made," Bouie said.

CDR Virginia Giroux, at the time a regulatory health project manager in the Division of Dermatologic and Dental Products, worked with the special needs population at the Orange County Convention Center. "Primarily, I worked in a triage area," Giroux said. "We conducted a quick assessment on any new arrivals to the shelter to evaluate their health status and placed them either in the general population or in the medical tent where they could be observed more closely. In addition we also evaluated any acute medical complaints from the residents in the general population. They were either released back to the general population or transferred to a local hospital for more definitive medical care."

Giroux offered one assessment of her experience that was shared by the others interviewed: "It was challenging figuring out our roles and getting down to work." All indicated that they were ready and willing to go on the next deployment.

"We have message after message from hospital administrators, Red Cross personnel, the Federal Emergency Management Agency's Federal Coordinating Office and county environmental health offices thanking us all for the wonderful work our officers did on their behalf," Babb said.

He recalled what the chief medical officer at the Sacred Heart Hospital in Pensacola told him after Hurricane Ivan made landfall and some Corps officers provided support to the hospital: "I've always heard that the best thing you can hear during wartime is: 'We're the Marines and we're here to help.' But now I've learned that during a disaster, the best thing you can hear is: 'We're the Public Health Service, and we're here to help.'"

CDER employees step lively in OWH Fitness Challenge

(Continued from page 3)

walked."

Whetstone set a goal of walking 10,000 steps, or about 5 miles, a day. "I'm very proud that I achieved that goal," she said. One of the ways she did it was by walking for 30 minutes at lunch every day. "I do feel more fit and am motivated to keep going. I've signed up for a dance class where we dance for an hour twice a week, and I'm going to continue to walk at lunch," she said.

The captain of the "Fitness Enforcers," Jones, who is the deputy director in the Office of Compliance, has also signed up for the Healthy Feds challenge. "I don't just feel fitter from the OWH Fitness Challenge—I am healthier, more energetic, and I've lost 25 pounds," Jones said.

Bond, a pharm/tox reviewer and a member of the CDER 570 4K Steppers, was also full of enthusiasm after completing the challenge. "I feel more fit, and I lost enough weight that even my supervisor noticed," he said. "I'd like to start another challenge right away—I would like to get even more fit and lose more weight."

Chakravarty, who is director of the Biologics Therapeutics Statistical Staff, noted that her baseline was just around 3,500 steps a day. "At the end of the challenge I was up to about 13,000 steps a day. It was a 170 percent improvement," Chakravarty said.

She reports feeling more energized and that she lost 7 pounds.

"The hardest thing was to keep it going after we crossed the middle point," Chakravarty said.

"I just told myself every small step counts and keep going. I would do small things to take more steps—walk to Parklawn, walk in a group during lunchtime, park at the farthest spot, get on a treadmill—so that I met my goals in bite-sized pieces."

The winners indicated they plan to try to continue living a fit lifestyle. As Lewis said, "I've still got my dog."

Highlights include new offices for Oncology, Non-Prescription Products

(Continued from page 1)

Office of Drug Evaluation II

- Division of Metabolism and Endocrinology Products
- Division of Pulmonary and Allergy Products
- Division of Analgesics Anesthetics, and Rheumatology Products

Office of Drug Evaluation III

- Division of Reproductive and Urology Products
- Division of Gastroenterology Products
- Division of Dermatology and Dental Products

Office of Antimicrobial Products (ODE IV)

- Division of Anti-Infective and Ophthalmology Products
- Division of Special Pathogen and Immunology Products
- Division of Anti-Viral Products

Office of Non-Prescription Products

- NDA product staff
- Monograph product staff

Minor changes in the **OND Immediate Office** will include the addition of a new biologics regulatory affairs team to assist in coordinating regulatory issues and ensuring consistency for therapeutic biologics products.

Creation of the new **Office of Oncology Products** brings together a critical mass of applications and staff focused on the development of new drugs for the diagnosis, treatment and prevention of cancer. This change will help us build on our excellent track record in this area and facilitate development of additional expertise and consistency in the rapidly growing field of chemoprevention.

The office will include a new cross-center Oncology Program that will coordinate the development and implementation of policy in the oncology area across FDA. The Oncology Program will also serve as a vital linkage among FDA and the National Cancer Institute, oncology professional organizations and the academic community.

ODE I will continue to include the Division of Cardiovascular and Renal Products. The separation of the Division of Neurology Products and the Division of Psychiatry Products will allow us to relieve some of the heavy workload pressures in the current Division of Neuropharmacologic Drug Products. Keeping these two new divisions within the same ODE will facilitate their continued close interaction and allow the current highly skilled clinical safety team to remain intact and to advise both divisions.

ODE II will continue to include the Division of Pulmonary and Allergy Products and the Division of Metabolism and Endocrinology Products. A new Division of Anesthesia, Analgesia and Rheumatology Products will bring these closely related and often overlapping medical areas and products into one division. This new division will be formed by combining product groups and reviewers from the current Division of Anesthetics, Critical Care and Addiction Drug Products and the current Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products.

ODE III will continue to include the Division of Reproductive and Urology Products and the Division of Gastroenterology Products. The office will also include the Division of Dermatology and Dental Products.

ODE IV will change little. The only major change will be the addition of the ophthalmology products and their reviewers to the current Division of Anti-Infective Drug Products to create a new Division of Anti-Infective and Ophthalmology Products.

The new **Office of Non-Prescription Products** will incorporate the product assignments for the current Division of Over the Counter Drug Products and will be aligned into two staff groupings: one for NDA products and one for monograph products. Over time, this new office will assume primary review responsibility for INDs and NDAs for non-prescription products while still working in concert with other review divisions as warranted.

In keeping with the goals for the consolidation of therapeutic biologics announced two years ago, applications for drugs and biologics will be assigned to review divisions based on the proposed therapeutic indication. This will enhance our ability to provide consistent advice to applicants in a given therapeutic area and provide exciting new opportunities for our reviewers to keep abreast of the latest scientific and regulatory developments.

In working on the reorganization, we developed a new workload model that allows more consistent and accurate estimates of divisional workload. The workload model will permit us to allocate resources to divisions in the future more fairly.

We plan to monitor workload trends on a yearly basis using a three-year rolling average of work for each division and OND in total and use this information to make decisions regarding allocation of new and existing reviewers. This annual review and readjustment of resource allocations will help us to meet our goal of better balancing the allocation of resources and work.

John Jenkins and Sandra Kweder are the OND director and deputy director respectively.

Pike's Puzzler: Clued-in definitions

BY TONY CHITE

Given the definition and the clues, what is the word?

1. Located away from normal position, as in pregnancy (seven-letter word; fourth letter is an "o").
2. A term used to describe behavior characterized by well-systematized delusions of persecution, delusions of grandeur, or a combination of the two (eight-letter word; sixth letter is an "o").
3. Deprived or destitute of water (nine-letter word; seventh letter is an "o").
4. A surgical operation on the nose, either reconstructive, restorative or cosmetic (11-letter word; fifth letter is an "o") .
5. These elements of a closely related chemical family are bromine, chlorine, fluorine, iodine, and astatine. (Eight letter word (in plural); fourth letter is an "o")

Answer key 1. ectopic; 2. paranoia; 3. anhydrous; 4. rhinoplasty; 5. halogens.

Tony Chite is a pharmacist in Olney, Md.

Nurses' everyday jobs at CDER help promote safe use of drugs

(Continued from page 1)

"The review team may consult the labeling to Division of Medication Errors and Technical Support in ODS for additional recommendations on labeling for safety and error prevention. The review team may request pictorials to demonstrate correct usage of the product, or additional pieces of labeling for further clarification such as a patient instruction booklet or a demo product."

A clinical background infectious diseases, HIV and public health serves **Tia Frazier, R.N., M.S,** well as she manages a diverse array of over-the-counter drug products. "I am very excited to have had the opportunity to provide both regulatory guidance and clinical insight in our work with topical antiseptic products used to prevent hospital-acquired infections," she said.

Cathryn Lee, MSN, CRNP, AOCN, said that her work in the Office of Drug Evaluation VI originally focused exclusively on addressing post-marketing commitment submissions related to biologic products.

"Many of these commitments are intended to address safety and efficacy questions not yet answered at the time of product approval," she said.

"Many sponsors were not submitting annual reports and final reports on post-marketing commitments as required in the regulations. In addition, there was a backlog in the review of submissions already submitted. Consequently, CDER's publicly available Web site for post-marketing commitments was not up-to-date. Clearing the backlog and encouraging the sponsors to comply with the regulations allows for the collection of important data on the biologic products."

Virginia Giroux and Jane McCarthy, co-chairs of the CDER Nurses Network, are a training specialist and scientific education team leader, respectively, in the Division of Training and Development.

CDER Nurses Network brings educational outreach to nursing groups

The CDER Nurses Network, an educational outreach program sponsored by the Office of Training and Communications, furthers the Center's mission to improve the safety of patients taking medicine.

Our goal is to educate nurses in the community by giving FDA lectures both locally and nationally to nursing groups at hospitals, universities, professional meetings and other places where nurses are educated. We identify Center nurses and how they use their nursing experience in their work.

There are currently 35 nurses in the network. They work in various positions from project managers in review divisions to consumer safety officers in postmarketing surveillance. If you are a nurse in CDER and interested in helping the Nurses Network in its outreach efforts, please contact **Virginia Giroux** or **E. Jane McCarthy.** In addition to us, here are the current members:

- **Sandra Birdsong, R.N., BSN,** Division of Drug Risk Evaluation, Office of Drug Safety.
- **Cheryl Ann Borden, R.N.,** Division of Cardio-Renal Drug Products, Office of Drug Evaluation I.
- **Johanna Clifford, R.N., BSN, M.S.,** Advisors and Consultants Staff, Office of Executive Programs.
- **Felecia Curtis, R.N., BSN,** Division of Dermatologic and Dental Drug Products, ODE V.
- **John David, R.N., BSN, M.S. in HRM,** DCRDP, ODE I.
- **Jane Dean, R.N., MSN, CCRC,** Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, ODE V.
- **Felicia Duffy, R.N., BSN,** Division of Medication Errors and Technical Support, ODS.
- **Cynthia Fitzpatrick, R.N., BSN,** Division of Public Affairs, Office of Training and Communications.
- **Joan Flaherty, R.N., MSN,** Division of Counter Terrorism, Office of Counter Terrorism and Pediatric Drug Development.
- **Tia Frazier, R.N., BSN, M.S.,** Division of Over-the-Counter Drug Products, ODE V.
- **Susan Giuliani, R.N., MSN, APRN, B.C.,** Division of Review Management and Policy, ODE VI.
- **Cathy Groupe, R.N., BSN,** ACS, OEP.
- **Rita R. Hassall, R.N., BSN, MSN,** Office of Generic Drugs, Office of Pharmaceutical Science.
- **Deborah J. Henderson, R.N., MSN,** Office of Executive Programs.
- **Ele Ibarra-Pratt, R.N., MPH,** Division of Scientific Investigations, Office of Medical Policy.
- **Juliaette Johnson,** Division of Compliance Risk Management and Surveillance, Office of Compliance.
- **Alice Kacuba, R.N., MSN, RAC,** Division of Gastrointestinal and Coagulation Drug Products, ODE III.
- **Lorene M. Kimzey, RNC, M.Ed.,** ODE IV.
- **Karen Kirchberg, N.P.,** Division of Reproductive and Urologic Drug Products, ODE III.
- **Patricia Knight,** DRUDP, ODE III.
- **Carol Krueger, R.N., BSN,** DCRMS, OC.
- **Cathryn Lee, CRNP, MSN, AOCN,** Division of Therapeutic Biological Oncology Products, ODE VI.
- **Terri Rumble, R.N., BSN,** ODE V.
- **Kenny Shade, J.D., BSN,** Division of Anti-Viral Drug Products, ODE IV.
- **Laura Shay, C-ANP, M.S.,** DOTCDP, ODE V.
- **Dornette D. Spell Lesane, R.N., NP-C, MHA,** ACS, OEP.
- **Dianne Tesch, RNP, BSN,** DSI, OMP.
- **Cheryl Turner, R.N., BSN,** DCT, OCTAP.
- **Holly Wieland, R.N., BSN, MPH,** Division of Metabolic and Endocrine Drug Products, ODE II.
- **Mary E. Willy, Ph.D.,** Division of Drug Risk Evaluation, ODS.
- **Linda Wisniewski, R.N., BSN, M.S., R.N.C, CCRN,** DMETS, ODS.
- **Su Yang, R.N., MSN,** DCT, OCTAP.
- **Karen Young, R.N., BSN,** DSRCS, ODS.

—Virginia Giroux and E. Jane McCarthy