news along the pike

NOVEMBER 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

VOLUME 11, ISSUE 2

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Center ceremony honors 107 individuals, 47 groups

Spring event inaugurates Frances Kelsey Drug Safety Award

BY JACKIE BARBER WASHINGTON

During CDER's Spring Honor Awards Ceremony, the Center's top managers presented 107 individual awards and 47 group or team awards. Kevin Barber sang the National Anthem. **Pat Gathers,** from the Office of Management, was the mistress of ceremonies. **Center Director Steven K. Galson, M.D., MPH,** and Deputy Center Director **Douglas Throckmorton, M.D.,** presented the awards along with CDER's senior staff.

"I am very pleased to have established the Dr. Frances O. Kelsey Drug Safety Excellence Award and to recognize the first recipients for their outstanding accomplishments in this important aspect of drug regulation," Dr. Galson noted. "I am inspired by the dedication and commitment of our talented staff."

The awards presented at the ceremony were:

FDA Outstanding Service Award

Edward Cox, M.D.

Gelind Creath

Katrina Garry

Venkateswar Jarugula, Ph.D.

Colleen Pritchard

Xiaoxing Wei, M.D.

FDA Leveraging/Collaboration Award

FDA-NIAID Radiological-Nuclear Countermeasures Group: **Larry Cress, M.D., Brad**

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Office of Biotechnology Products tackles transition

BY STEVEN KOZLOWSKI, M.D.

With the move of CDER's reviewers to White Oak this summer and fall, the clinical review of therapeutic biological products has become formally integrated into the Center's traditional discipline-oriented structure. Because our office—the Office of Biotechnology Products—has primary review responsibility for therapeutic biologics quality issues and will remain in Bethesda, we want to take this opportunity to introduce the rest of CDER to:

- The scope of therapeutic biological products.
- The scientific issues with biologic product quality.
- Our reliance on process controls in manufacturing.
- The important regulatory role of understanding a biologic product's mechanism of action.
- Special concerns with biologics adverse events.
- Our plans for enhanced communications with CDER reviewers.

(Continued on page 4)

Regulation requires electronic Structured Product Labeling

A regulation effective Nov. 2 requires drug manufacturers to submit prescription drug label information in an electronic format. Called Structured Product Labeling, or SPL, this format will allow health-care providers and the general public easier access to the product information found in the FDA-approved package inserts, or "labels," for all approved medicines in the United States.

The new electronic product labels will be the key element and primary source of medication information for DailyMed. This interagency online health information clearinghouse will provide the most up-to-date medication information free to consumers, health-care providers and health-care information providers. Within one year, product labels for most approved prescription medications will be posted on DailyMed.

DailyMed will be accessed through the National Library of Medicine at http://dailymed.nlm.nih.gov. In the future, this new product information will also be posted on a

(Continued on page 5)

JOE'S NOTEBOOK

NCTR to study liver toxicity biomarkers

FDA's National Center for Toxicological Research and BG Medicine, a Massachusetts-based biotechnology research company, have agreed to collaborate on jointly conducting a liver toxicity study. The Liver Toxicology Biomarker Study is designed to overcome one of the primary obstacles to the efficient development of safe and effective drugs. It aims to discover biomarkers of human hepatotoxicity in the standard tests used by pharmaceutical manufacturers in the initial stages of drug development.

Liver toxicity is the most common biological reason for drug failure in the development of new pharmaceuticals. It affects one in six drugs in development. The toxicity tests currently in use by drug companies have been unchanged for at least 40 years and often fail to identify human liver toxicity issues. Consequently, liver toxicity is often detected for the first time when drugs are in Phase 2 of clinical testing after tens of millions of dollars or more have been spent on a drug's development.

Early detection of potential safety problems is one of the main objectives of the Critical Path Initiative, which seeks to modernize drug development by making the process more predictable, successful and less costly. The proposed project addresses the liver toxicity issue highlighted in the Critical Path document as one of the obvious and priority areas for innovation.

"Liver toxicity is a common reason for drug development failure," said FDA Deputy Commissioner for Operations **Janet Woodcock, M.D.** "In part, this is due to the fact that the safety evaluation relies on decades-old technologies that may recognize safety problems only after extensive clinical studies. By identifying biomarkers for liver toxicity at the start of the development process, this research should yield important benefits for industry, the FDA and the public."

Dr. Woodcock is the principal author of FDA's March, 2004 report, *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products.*

The CRADA procedure routinely governs FDA's collaborative studies with the private sector. The Liver Toxicity Biomarker Study has been designed by FDA and BG Medicine with input from other pharmaceutical companies and will be conducted, with their collaboration, at the NCTR laboratory in Jefferson, Ark., and BG Medicine in Waltham, Mass.

Participating companies will receive access to all project data and a perpetual license to any biomarkers that are discovered.

Corrections. Some photocopies and the initially posted Internet versions of the April *News Along the Pike*, contained errors in the awards listings.

In the story about the FDA Science Forum, some incorrect information appeared for **Joan Buenconsejo, Ph.D.,** who was nominated by CDER for the Outstanding Junior Investigator Award.

In the main awards story, **Gregory M. Dubitsky, M.D.,** received a CDER Excellence in Mentoring Award and **Robert Harris, M.D.,** received a CDER Excellence in Leadership Award. The names and awards had been inadvertently reversed. The Internet versions are now correct.

Dec. 1: World AIDS Day. An estimated 39.4 million people worldwide were living with HIV at the end of 2004, and more than 20 million people have died of AIDS since 1981. With more than 1 million HIV-positive individuals in the United States and 35,000 to 40,000 new infections every year, our country, like other nations around the world, is deeply affected by HIV/AIDS. HHS encourages you to visit its Web site and download World AIDS Day educational materials at http://www.omhrc.gov/hivaidsobservances/world/.

news along the pike

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

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

Photocopies are available in the FDA Biosciences Library in the Parklawn Building, Room 11B-40, and its White Oak Branch on the ground floor of Building 22, Room 0443.

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NEWS ALONG THE PIKE
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DARRTS

Integrated document database targets therapeutic biologics INDs

By Virginia Ventura

If you're a biologics reviewer, you will soon be pioneering a new software program called DARRTS. No, not the little pointy things you throw, but a system that will ultimately act as the Center's main repository of regulatory documents.

DARRTS stands for Document Archiving, Reporting and Regulatory Tracking System. This single, integrated system will eventually house many of the Center's core tracking systems, such as:

- Components of the Centerwide Oracle Management Information System or COMIS.
- The Division Files System or DFS.
- CDER Standard Letters or CSL.

However, the first release of DARRTS, planned for this winter, will target only investigational new drug applications for therapeutic biologic products. Only reviewers and project managers working on biologics IND reviews—primarily former users of the Biologics Investigational New Drug Management System—will use the software in this first release.

(Unfortunately, there is a great deal of overlap between the therapeutic biologic IND numbers and older, existing IND numbers for drugs. On Nov. 11, current CDER INDs numbered 14,000 and below will be renumbered by taking the existing IND number and adding 80,000 to it. Most CDER INDs in that number range are largely withdrawn, terminated or otherwise inactive.)

Over the next couple of years, DARRTS will be expanded to all users throughout the Center and will cover most other submission types, including new drug applications, generic drug applications, biologics license applications and other investigational new drug applications.

The DARRTS working group at CDER has collaborated closely with developers over many months to craft this completely redesigned database.

The new system strives to allow you greater flexibility and eliminate some of the familiar work-arounds that you have had to grapple with.

A sampling of DARRTS highlights includes:

- Web-based, single sign-on.
- Application numbers automatically generated.
- Incoming document data entry done by document room (except for single-patient INDs with authorization).
- Division staff ability to create emergency INDs.
- All updates based on transmittal form information or project manager notifications performed by document room staff, not reviewers.
- Goals, statuses, assignments and other standard data automatically maintained by system.
- No system codes to memorize or worry about deciphering.

Information on training will be conveyed by e-mail, and all training materials will be posted on the CDER intranet. Training will consist of two parts:

- Conceptual training, to be held in the mornings.
- Classroom demonstration, usually in the afternoons.

Since DARRTS concepts are so different from those used by the current systems, it's important for you to attend the conceptual session and to ask questions of the experts. The classroom demonstration that follows will take into practice the points discussed in conceptual training. There will be a total of 10 overall training sessions, open to reviewers involved with biologics INDs.

For more information on DARRTS training please contact me at 301-796-1016 or e-mail Virginia.Ventura@fda.hhs.gov.

For information on the DARRTS project in general, contact **Linda Sigg** at 301-796-0625 or Linda.Sigg@fda.hhs.gov.

Virginia Ventura is a member of the Regulatory Review Support Staff in the Office of Business Process Support Staff.

Information Technology Corner

New version of Substance Registration System key to structured labeling

By Binh Ta, Colleen Ratliffe and Sandra Valencia

A new version of the Substance Registration System/Ingredient Dictionary soon will be available for use as a key component of the Structured Product Labeling program (page 1).

The dictionary has been designed to enable FDA to efficiently, effectively and reliably maintain unique identifiers for substances in drugs, biologics, foods and devices.

When implemented, the system will help FDA and the medical communities standardize substance data by generating the Unique Ingredient Identifier.

This identifier will be incorporated into labeling submissions through FDA's Electronic Labeling Information Processing System. That system will modernize the way labels are submitted, reviewed and distributed. The public will access labeling through the National Library of Medicine's Web site.

The overall purpose of the structured product labeling program is to improve patient safety by ensuring that the most up-to-date medication information is available to health-care providers, patients and the public. The project is part of a larger initiative called the DailyMed. The DailyMed Initiative, supported by the Agency for Healthcare Research and Quality, is a partnership between FDA, medication manufacturers and distributors, the National Library of Medicine and health-care information suppliers.

For more information on FDA's Substance Registration System, please go to the FDA Data Standards Council intranet site at http://intranet.fda.gov/oc/fdadatacouncil/proj.htm and click on the Vocabulary Standards link at the bottom of the page.

Binh Ta, Colleen Ratliffe and Sandra Valencia are IT specialists in the Office of Information Technology.

Office of Biotechnology Products addresses issues of quality

(Continued from page 1)

Biologics A to Z

When oversight of therapeutic biologics officially transferred to CDER in 2003, review responsibilities were divided between the Office of New Drugs and the Office of Pharmaceutical Science.

Our office—the Office of Biotechnology Products in OPS—has primary review responsibility for chemistry, manufacturing controls and product quality.

We have approximately 60 licensed products from Activase (alteplase) to Zevalin (ibritumomab tiuxetan). Among them are:

- Erythropoetins, widely used for treatment of anemia induced by chemotherapy and renal disease.
- Interferons, used for a number of different indications from malignancy to hepatitis.
- Fusion proteins and antibodies that target inflammatory mediators, such as tumor necrosis factor.
- Monoclonal antibodies that target molecules on the surface of tumor cells. Examples are antibodies targeting epidermal growth factor receptor and Erb2.

These products improve survival times and/or quality of life in a variety of diseases, and there are hundreds of new products under development. Despite an overall slowing in development of new molecular entities, many biotechnology product classes have an increasing product pipeline.

Biotechnology products comprised approximately $30 billion of the $400 billion in worldwide pharmaceutical sales in 2002. The biotechnology percentage of worldwide pharmaceutical sales is increasing. Estimates of biotechnology are that sales in 2004 exceeded $40 billion dollars. In addition to their current role as monotherapy, proteins are likely to play important future roles in combination therapies and in conjunction with cellular and nano-technologies.

Product quality scientific issues

There are a large number of scientific issues in the manufacture and quality control of therapeutic proteins. Unlike many small molecule drugs, often our products cannot be fully characterized using traditional physical or chemical methods. For many of our products, it is infeasible to have a complete evaluation of product's structure or even how many active molecules it contains.

This leads to complex regulatory decisions regarding "sameness" of protein therapeutics. These issues extend beyond protein chemistry into broader areas of protein function and biology.

Often, comparability is a relative assessment that requires information on the amount of clinical and pre-clinical information being transferred from the old to the new version of the product. Successful science-based regulatory decisions have depended on and will continue to depend on close interactions between the review disciplines.

Importance of manufacturing controls

The difficulties in characterizing therapeutic proteins have led to a greater dependence on a controlled manufacturing process. Because of the importance of facilities in a consistent manufacturing process, the Therapeutics Facilities Review Branch in the Office of Compliance plays a significant role in the evaluation of biotechnology products (July 2004 *Pike*).

The important role of process in all pharmaceutical manufacturing is being recognized with initiatives such as cGMPs for the 21st Century and Process Analytical Technology. Although biotechnology product manufacturing has historically focused on process, there are many areas for improvement with real-time monitoring and control of both critical process parameters and product attributes.

Inherent to these improvements is an understanding of the important product attributes for safety and efficacy. This is a very challenging task for all products and especially for complex mixtures of proteins. The biological characterization of proteins and the understanding of structure and function relationships are important in making informed decisions.

Because of the lack of certainty regarding structure, biological tests are commonly used to evaluate our products. Ideally, these assays should reflect the molecular mechanism of action. Knowledge about a product's mechanism of action is important for regulating applications in a context broader than the assessment of manufacturing quality.

Role of molecular mechanisms

Molecular mechanisms cannot replace clinical data but may be of value when there are inadequate clinical data to make a decision. Shared mechanisms may alert us to potential adverse events. For many therapeutic proteins, adverse events are due to the primary mechanism of action. Therefore, mechanistic information can provide a critical context for informed decisions regarding product safety.

In some cases, mechanistic information can facilitate selection of relevant animal models and speed products along the Critical Path (July 2004 *Pike*). Many of our reviewers are biologists and some are pharmacologists or physicians.

In addition, many of our reviewers perform bench research and publish in areas related to the products they review. A list of contacts for mechanistic and technical issues has been placed on our intranet site (http://cdernet.cder.fda.gov/ops/opsdiscp.htm) and distributed to the review divisions.

In the future, advances in systems biology will allow for more "personalized medicines" (April 2005 *Pike*) and facilitate clear decisions on drugs with far smaller numbers of patients needed in clinical trials. The understanding of biological mechanisms can facilitate use of data sets such as those provided by proteomics or pharmacogenomics.

In many clinical studies, the numbers leading to an association of a clinical outcome with a set of markers may not be statistically convincing. The mechanistic context of these markers, however, may add confidence to their validity and further use.

We can play a role in helping you make an assessment of biological plausibility. Therefore, we have begun planning interactions with the Interagency Pharmacogenomics Review Group (April *Pike*).

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SPL key to providing free Web access for up-to-date Rx labeling

(Continued from page 1)

comprehensive Internet resource—Facts@fda.gov—that will give one-stop access to information about all FDA-regulated products.

The SPL project, led by CDER, is the first in an Agencywide initiative regarding the public provision of electronic information. In the future DailyMed also will include labels for biologics (such as vaccines), medical devices, veterinary drugs and some food products. The agency expects to launch additional components of the facts@fda.gov Internet resource early next year.

"Providing health-care providers and patients with clear, concise information about their prescriptions will help ensure safe use of drugs and better health outcomes," said Health and Human Services Secretary **Mike Leavitt.** "Now medication information will be easy to access on a publicly available Web site, and this will lead to future innovations with health information technology."

Under the new regulation, drug manufacturers are required to submit prescribing and product information in SPL format. This accessible, computer readable format will help provide accurate, up-to-date drug information using standardized medical terminology.

Using embedded computer tags, the prescribing and product information in SPL can be electronically managed, allowing searches for specific information. These tags can instruct computers to read specific sections of a drug label including product names, indications, dosage and administration, warnings, description of drug product, active and inactive ingredients and how the drug is supplied.

With this information, physicians will be able to quickly search and access specific information they need before prescribing a treatment.

In addition, having the labels submitted in SPL will improve the drug labeling review process. In turn, we can provide doctors and patients faster access to the most recent information about medications.

As FDA receives SPL-formatted labeling, health-care professionals, patients, online information providers and other consumers will be able to access the newly updated labels on the Internet, free of charge through the DailyMed system.

Updated product labels will be posted on the site within one business day of either an approval action or a submission of a labeling change that does not require an approval.

"This unprecedented health technology partnership builds a solid foundation for enhanced e-health initiatives to be realized in the very near future," said Acting FDA Commissioner **Andrew von Eschenbach, M.D.**

"The electronic standards established with structured product labeling pave the way for future health information innovations in areas such as electronic prescribing and electronic health record keeping, that can transform the way we gather, use and share medication information from bench to bedside."

The DailyMed system was developed in collaboration with federal agencies including: FDA, the National Library of Medicine, the Agency for Healthcare Research and Quality and the National Cancer Institute in the Department of Health and Human Services and the Veterans Health Administration in the Department of Veteran Affairs.

The SPL initiative is part of an ongoing collaboration of federal agencies to apply modern principles of information science to translate, repackage and freely distribute up-to-date medication information in a reliable, accurate and consistent format. The group is dedicated to building a nationwide infrastructure for managing medication information to improve healthcare quality in the United States.

OBP plans improved communications with biologic reviewers in OND

(Continued from page 4)

Immune system responses

Another important issue relevant to protein therapeutics is their potential to be recognized as foreign by a patient's immune system. In some cases, immune responses to a protein product have led to neutralization of the patient's own version of the protein.

In the case of erythropoetin, for example, such immune responses have left some patients unable to make red blood cells, a condition known as transfusion-dependent pure red cell aplasia or PRCA. Of note, increased occurrences of PRCA were associated with a manufacturing change of the product distributed in Europe.

This reinforces the strong relationship between clinical and manufacturing review disciplines. Our office has many experts in immunology who are well-known in both academia and industry.

They are a valuable resource for general approaches to immunogenicity and for evaluation of assays to detect immunogenicity.

We also will be placing our point of contact for immunogenicity issues on our intranet site and passing it out to Center offices and divisions.

Although most of CDER's review staff has moved to White Oak, our offices and labs will remain on the NIH campus in Bethesda for a few more years. Although there are many advantages to having access to NIH researchers, conferences and libraries, we will have some challenges in communicating with other parts of CDER. From collaborating with two clinical divisions in one office, we will now need to communicate with 13 divisions in five offices.

We plan to have primary and secondary contacts for assignments. Once assigned, our reviewer will be the primary contact for product-related questions.

In addition, we have assigned each OND office an umbrella contact who will spend one day a week at White Oak. Details on these contacts are also included on our intranet site (http://cdernet.cder.fda.gov/ops/opsdiscp.htm).

We are interested in feedback on our interactions with other offices in CDER. We look forward to working closely with you to ensure that quality pharmaceutical products are available to the public.

Steven Kozlowski is acting director of the Office of Biotechnology Products.

CDER awards ceremony honors 107 individuals, 47 groups

(Continued from page 1)

Leissa, M.D., Alla Shapiro, M.D., and Cheryl Turner. PHS officers nominated for companion award: **CDR Mitchell Mathis, LCDR Narayan Nair and CPT Mary Purucker.**

Interagency List Development Group: **John Alexander, M.D., Debbie Avant, Melisse Baylor, M.D., ShaAhvree Buckman, M.D., Jane Filie, M.D., Larry Grylack, M.D., Abraham Karkowsky, M.D., Carl Kraus, M.D., Tamar Lasky, Ph.D., Jill Lindstrom, M.D., Jane Leahey, Lolita Lopez, M.D., Donald Mattison, M.D., Susan McCune, M.D., Joette Meyer, Pharm.D., Bindi Nikhar, M.D., Andrea Pikis, M.D., William Rodriguez, M.D., Hari Sachs, M.D., Alan Shapiro, M.D., Philip Sheridan, M.D., Thomas Smith, M.D., Kathie Robie Suh, M.D., Jean Temeck, M.D., Celia Winchell, M.D.,** and **Carolyn Yancey, M.D.** PHS officer nominated for companion award: **CDR Lisa Mathis.**

FDA Plain Language Award

Sandhya Apparaju, Ph.D.

CDER Standard Letters Committee: **Amy Baird, Bronwyn Collier, Jean Dean, Michael Folkendt, Enid Galliers, Gary Gensinger, Glen Jones, Frances LeSane, Lisa Malandro, Cathleen Michaloski, Connie O'Leary, Leah Ripper, Besty Scroggs, Patricia Stewart, Victoria Tyson Medlock** and **Maria Walsh.** PHS officers nominated for companion award: **LT Richardae Taylor, CDR Jacqueline Ware** and **LCDR Samuel Wu.**

FDA Quality of Work Life Award

Rose Smith

FDA Group Recognition Award

Ciprofloxacin Pediatric Use Review Team: **Renata Albrecht, M.D., Steven Gitterman, M.D., Stephen Hundley, Ph.D., Joette Meyer, Pharm.D., Yon Yu, Pharm.D., Peter Dionne, Ph.D., Rigoberto Roca, M.D., Ruthanna Davi, Karen Higgins, Philip Colangelo, Pharm.D., Ph.D., Dakshinia Chilukuri, Dorota Matecka, Ph.D., Karen Storms** and **Mathew Thomas.** PHS officers nominated for companion award: **CAPT Leslie Ball** and **CDR Lisa Mathis.**

Decorporation Agents Working Group: **Julie Beitz, M.D., Siham Biade, Ph.D., Young-Moon Choi, Ph.D., Larry Cress, M.D., Nancy Derr, Shahla Farr, Christy John, Ph.D., Donna Katz, J.D., Tushar Kokate, Ph.D., Adebayo Laniyonu, Ph.D., David Place, Ph.D., Ramesh Raman, M.D., Patricia Stewart, Orham Suleiman, Ph.D., Mike Welch, Ph.D.,** and **Robert Yaes, M.D.** PHS officer nominated for companion award: **CDR Mitchell Mathis.**

Doc-U-Ask Team: **JoAnn Berger, Lee Bernstein, Wendy Chang, Jennifer Coakley, Darlene Gilbert, Lynette Gray, Rinaldi Jachja, Rebecca Jacob, Sharon Marcus, Nancy Martinez, Kathrin McConnell, Susan Mixon, Colleen Pritchard, John Stephens** and **Elizabeth Wack.**

End of Phase 2A Group: **Vikram Arya, Ph.D., Jogarao Gobburu, Ph.D., Kendall Marcus, M.D., Lisa Naeger, Ph.D., J. Robert Powell, Pharm.D., Kellie Reynolds, Pharm.D., Meiyu Shen, Ph.D., Fraser Smith, Ph.D., Guoxing Soon, Ph.D., Kim Struble, Pharm.D., Yaning Wang, Ph.D.,** and **Jenny Zheng, Ph.D.** PHS officer nominated for companion award: **LCDR Vasavi Reddy.**

Palifermin Review Team: **Ralph Bernstein, Ph.D., Wiley Chambers, M.D., Pat Dinndorf, M.D., Susan Giuliani, Joseph Gootenberg, M.D., Karen Hirshfield, Colleen Hoyt, Karen Jones, Lisa Kammerman, Ph.D., Patricia Keegan, M.D., Jianming Li, Ph.D., Anita O'Connor, Ph.D., Mark Rothmann, Ph.D., Emily Shacter, Ph.D., Yuan Li Shen, Ph.D., Kurt Stromberg, Ph.D., Marlene Swider, Ph.D., Jose Tavarez-Pagan, Barbara Wilcox, Ph.D.,** and **Hong Zhao, Ph.D.** PHS officer nominated for companion award: **CAPT John Kelsey.**

Tinidazole Review Team: **Renata Albrecht, M.D., Regina Alivisatos, M.D, Shakal Bala, Ph.D., Christina Chi, Ph.D., Philip Colangelo, Pharm.D., Ph.D., Edward Cox, M.D., MPH, Gerlie Gieser, Ph.D., Karen Higgins, Stephen Hundley, Ph.D., Carl Kraus, M.D., Dorota Matecka, Ph.D., Leonard Sacks, M.D., Norman Schmuff, Ph.D., Kalavaty Suvarna, Ph.D., Maureen Tierney, M.D.,** and **Martin Yau, Ph.D.** PHS officers nominated for companion award: **LT Jinhee Jahng** and **LT LaRee Tracy.**

Tysabri for Multiple Sclerosis Review Team: **Wilson Bryan, M.D., Beverly Conner, Pharm.D., Catherine Gray, Pharm.D., Elena Gubina, Ph.D., Koti Kallappa, Ph.D., Calvin Koerner, Joseph Kutza, Ph.D., Iftekhar Mahmood, Ph.D., Cathleen Michaloski, MPH, Anne Pilaro, Ph.D., Patrick Swann, Ph.D., Marc Walton, M.D., Ph.D., Barbara Wilcox, Ph.D., Zhang, Lei, M.D., Ph.D.,** and **Bo-guang Zhen, Ph.D.** PHS officers nominated for companion award: **CDR Carole Broadnax, CDR Charles Hoppes, CDR J. Lloyd Johnson** and **CDR Ellis Unger.**

Woodmont II Safety Evaluator Team: **Charlene Flowers, R.Ph., Cindy Kortepeter, Pharm.D., Susan Lu, R.Ph., Carol Pamer, R.Ph., Kate Phelan, R.Ph., Mary Ross Southworth, Pharm.D., Daniela Sanders** and **Lopa Thambi, Pharm.D.** PHS officer nominated for companion award: **CDR Robert Pratt.**

PHS Commendation Medals

LCDR Sean Belouin

CAPT Roger Goetsch

LT Kristen Miller

LCDR Nitin Patel

CDR Kevin Prohaska

CAPT Cathie Schumaker

CDR Ann Staten

LT Emily Thakur

Center Director's Special Citation

Min Chen, Pharm.D., MPH

Mary Dempsey

Claudia Karworski, Pharm.D.

David Morley

Brian Pendleton

CAPT Paul Seligman

Office of Drug Safety Project Managers: **Sandra Birdsong** and **Mary Dempsey.** PHS officers nominated for companion award: **CDR Sammie Beam, LT Lisa**

(Continued on page 7)

Award named after long-time CDER employee Dr. Frances Kelsey

(Continued from page 6)

Hubbard, LT Robert Kang, LT Quynh Nguyen, LCDR Leslie Stephens, LT Tara Turner and **CDR Deborah Yaplee.**

Office of Legislation Drug Team: **Jeremiah Kelly, Patrick McGarery, Karen Meister, Michele Mital, Patrick Ronan, Bunny Rose-Lewis, Joy Stevens** and **Felecia Wooten.** PHS officer nominated for companion award: **CAPT Diane Prince.**

CDER Special Recognition Award

Wendy Aaronson

Sophia Abraham, Ph.D.

Mohamed Alosh, Ph.D.

Venkatesh Bhattaram, Ph.D.

Yuan Who Chen, Ph.D.

Beverly Conner, Pharm.D.

Patricia Cortazar

Kimberly Culley, Pharm.D.

Susan Cummins, M.D., MPH

Mehul Desai, M.D.

E. Carol Doyle

Elizabeth Duvall-Miller

Michael Evans, R.Ph.

Evelyn Farinas, R.Ph.

Donald Hare, R.Ph.

Sharon Hertz, M.D.

Karen Hicks, M.D.

Stanka Kukich, M.D.

Linda Kim-Jung, Pharm.D.

Frederic Marsik, Ph.D.

Satish Misra, Ph.D.

Ramsharan Mittal, Ph.D.

Hasmukh Patel, Ph.D.

Lin Qi, Ph.D.

Haripada Sarker, Ph.D.

Tawni Schwemer

Khin Muang U, M.D.

Yaning Wang, Ph.D.

Clinical Pharmacology/Pulmonary and Allergy Co-located Review Support Group: **Sayeed Al Habet, Ph.D.,** and **Sandra Suarez-Sharp, Ph.D.**

Division of Metabolic and Endocrine Drug Product Team: **Blair Fraser, Ph.D., Enid Galliers, Kati Johnson** and **Xavier Ysern, Ph.D.** PHS officers nominated for companion award: **CDR John Hill** and **CAPT Margaret Simoneau.**

Project Management Communications Committee: **Leonthena Carrington, Melissa Furness, Diane Moore, Margo Owens, Archana Reddy, MPH, Jacquelyn Smith** and **Monika Unger.** PHS officers nominated for companion award: **CDR Virginia Giroux, LT Valerie Jimenez, LCDR Monica Johnson, LT Andrei Nabakowski, LT Raquel Peat, LCDR Shelia Ryan, LCDR Stanley Shepperson.**

Prostate Cancer Endpoints Team: **George Benson, M.D., Donna Griebel, M.D., Pat Keegan, M.D., Bhupinder Mann, M.D., Richard Pazdur, M.D., Daniel Shames, M.D., Dianne Spillman** and **Grant Williams, M.D.**

CDER Dr. Frances O. Kelsey Drug Safety Excellence Award

Tarek Hammad, M.D., Ph.D.

Andrew Mosholder, M.D., MPH

CDR Deborah Yaplee

Division of Neuropharmacological Drug Products Safety Team: **Gerard Boehm, M.D., MPH, David Gan, M.D., Dr. PH., Tarek Hammad, M.D., Ph.D., Alice Huges, M.D., M. Lisa Jones, M.D., MPH, James Knudsen, M.D., Ph.D., Judith Racoosin, M.D.,MPH,** and **Marc Stone, M.D.**

Division of Pharmaceutical Evaluation II: **Hae-Young Ahn, Ph.D., Suliman Al-Fayoumi, Ph.D., Sayed Al Habet, Ph.D., Sandhya Apparaju, Ph.D., Julie Bullock, Pharm.D., Dhruba Chatterjee, Ph.D., Tien Mien Chen, Ph.D., Young Moon Choi, Ph.D., Sang Chung, Ph.D., Suresh Doddapaneni, Ph.D., Emmanuel Fadiran, Ph.D., John Hunt, Christy John, Ph.D., Leslie Kenna, Ph.D., Myong Jin Kim, Pharm.D., Shinja Kim, Ph.D., Sze Lau, Ph.D., David Lee, Ph.D., Sue Chih Lee, Ph.D., Henry Malinowski, Ph.D., Srikanth Nallani, Ph.D., Ting Eng Ong, Ameeta Parekh, Ph.D., Wei Qiu, Ph.D., Alfredo Sancho, Ph.D., Donald Stanski, M.D., Sandra Suarez-Sharp, Ph.D., He Sun, Ph.D.,** and **Jayabharath Vaidyanathan, Ph.D.,** and **Xiaoxiong Wei, M.D., Ph.D.** PHS officer nominated for companion award: **LT Stephan Ortiz.**

Zometa Safety Team: **Brian Booth, Ph.D., Jennie Chang, Pharm.D., Jogarao Gobburu, Ph.D., Lanh Green, Pharm.D., MPH, Amna Ibrahim, M.D., John Johnson, M.D., Carolyn, McCloskey, M.D., MPH, Carol Pamer, R.Ph., Richard Pazdur, M.D., Roshni Ramchandani, Ph.D., Nancy Scher, M.D.,** and **Grant Williams, M.D.** PHS officer nominated for companion award: **CDR Ann Staten.**

CDER Administrative/Program Management Excellence Award

Julie Basore

Patricia Carr

Karen Lucia

Maureen Majors

Jamie Metz

Matthew Zell

CDER Excellence in Communication Award

Melissa Bates

Mark Conliffe

Cecil Cupid

Gerald Feldman, Ph.D.

Mike Marino

Marilyn Pitts, Pharm.D.

Andre Raw, Ph.D.

Susmita Samanta, M.D.

John Simmons, Ph.D.

Marla Stevens-Riley, Ph.D.

Karen Young

AERS Quarterly Extract Team: **Lynette Swartz.** PHS officer nominated for companion award: **CDR John Quinn.**

CDER Participants in the 2004 Accelerating Anticancer Agent Development and Validation Workshop: **Brian Booth, Ph.D., Ramzi Dagher, M.D., Ann Farrell, M.D., Patricia Keegan, M.D., John Leighton, Ph.D., David Morse, Ph.D., Atiqur Rahman, Ph.D., Richard Pazdur, M.D., Mark Rothman, Ph.D., Gerald Sokol, M.D., Rajeshwari Sridhara, Ph.D., Lilia Talarico, M.D., Gene Wil-**

(Continued on page 8)

CDER awards ceremony honors 107 individuals, 47 groups

(Continued from page 7)

liams, Ph.D., Grant Williams, M.D., and **Peiling Yang, Ph.D.**

DODP Communications Team: **Brian Booth, Ph.D.,** and **Jogarao Gobburu, Ph.D.**

Follow-On Protein Pharmaceutical Planning Committee: **Janice Brown, Chi-Wan Chen, Ph.D., Barry Cherney, Ph.D., Blair Fraser, Ph.D., Theresa Gerrad, Ph.D., Dena Hixon, M.D., Christopher Joneckis, Ph.D., Gordon Johnston, R.Ph., Frank Holcombe, Ph.D., Kathleen Klouse, Ph.D., Steven Kozlowski, M.D., Stephen Moore, Ph.D., Gene Murano, Ph.D., Sara Radcliffe, MPH, Amy Rosenberg, M.D., Marie Vodicka, Ph.D.,** and **Keith Webber, Ph.D.** PHS officer nominated for companion award: **CAPT Marilyn Welschenbach.**

Office of Drug Safety Orientation Working Group: **Melissa Bates, Kath;y Farhat-Sabet, Evelyn Farinas, R.Ph., Katrina Garry, Lauren Lee, Pharm.D., Andy Mosholder, M.D., MPH, Rita Ouellet-Hellstrom, Ph.D., MPH, Tonia Piazza-Hepp, Pharm.D.** PHS officer nominated for companion award: **LT Nora Roselle.**

Pharmacogenomics Seminar Series Organizing Committee: **Ikram Elayan, Ph.D., Suzanne Fitzpatrick, Ph.D., Wafa Harrouk, Ph.D., Shwu-Luan Lee, Ph.D., John Leighton, Ph.D., Haleh Mahloogi, Ph.D., Karol Thompson, Ph.D., S. Leigh Verbois, Ph.D.,** and **Alexandra Worobec, M.D.**

Staff of the Division of Drug Information: **John Cesaletti, Gelind Creath, Barbara Daciek, Harold Davis, Edward Depaola, Donald Dobbs, Brenda Kiliany, Michael Ledley, Larry Lim, Barbara Palm** and **Joan Powers.** PHS officers nominated for companion award: **LCDR Renu Chhabra, CDR Mary Kremzner, LCDR Frederick Lockwood, LT Christine Oliver, LCDR Brenda Stodart, LCDR Hawyee Yan** and **LCDR Catherine Yu.**

CDER Leadership Excellence Award

Jerry Collins, Ph.D.

Jeri El-Hage, Ph.D.

Florence Fang

Zili Li, M.D., MPH

Richard Lostritto, Ph.D.

Stephen Miller, Ph.D.

Curtis Rosenbraugh, M.D., MPH

David Ross

Patrick Swann, Ph.D.

Marc Walton, M.D., Ph.D.

CDER Excellence in Mentoring Award

Rosemary Johann-Liang, M.D.

Lydia Martynec, M.D.

Katherine Needleman

Thomas Oliver, Ph.D.

Mary Parks, M.D.

Andrea Weir, Ph.D.

CDER Project Management Excellence Award

Michael Folkendt

Enid Galliers

Susan Giuliani

Barbara Gould

Kati Johnson

Margo Owens

Division of Anti-Infective Drug Products Project Management Staff: **Maureen Dillon-Parker, Susmita Samanta, M.D., Judit Milstein, J. Christopher Davi** and **Frances LeSane.**

Division of Over-the-Counter Drug Products Project Management: **Leah Christl, Ph.D., Walter Ellenberg, Ph.D.,** and **Tia Frazier.** PHS officers nominated for companion award: **CAPT Elaine Abraham, LCDR Keith Olin** and **CAPT Laura Shay.**

Executive Operations Staff: **Christine Bechtel, Rose Cunningham, Diane Ehrlich, Frances Gipson, Mark Gonitzke, Patrick Guinn, Anne Henig, Maureen Hess, Vikki Kinsey, Michele Lackner, Coralee Lemley** and **Theresa Martin.**

Therapeutic Biologics Internal Medicine Group: **Beverly Conner, Erik Laughner, Cathleen Michaloski, Florence Moore, Katherine Needleman, James Reese, Ph.D., Diane Sartor, Cristi Stark, Victoria Tyson-Medlock** and **Karen Winestock.**

CDER Regulatory Science Excellence Award

Karen DeBell

Roshni Ramchandani, Ph.D.

Wendy Weinberg, Ph.D.

Florian Zielinski

CDER Support Staff Excellence Award

Eda Howard

Chanta James

Lorraine Meaney

Christine Moser

Thuan Nguyen

Kim Robertson

Myrtle Shreve

Nadine Warren

Edward Washington

Kristin West

Mildred Williams

CDER Team Excellence Award

Bar Code Regulation Implementation Team: **Deborah Autor, Flora Chang, Herbert Gerstenzang, Robert Heller, John Loh, Frederic Richman, Margaret O'Rourke, Janice Steinschneider** and **Valerie Whipp.**

CDER/CBER WebVDME Pilot Implementation Team: **Renan Bonnel, Pharm.D., MPH, Marthe Bryant-Genevier, M.D., Dale R. Burwen, M.D., MPH, Min Chu Chen, R.Ph., Kathleen Farhat-Sabet, Hector Izurieta, M.D., MPH, Cindy Kortepeter, Pharm.D., Hyon Kwon, Pharm.D., MPH, Laruren Lee, Pharm.D., Carolyn McCloskey, M.D., MPH, Melodi McNeil, R.Ph., Rita Ouellet-Hellstrom, Ph.D., MPH, Marilyn Pitts, Pharm.D., Lise Stevens, Ana Szarfman, M.D., Ph.D., Melissa Truffa, R.Ph., Joyce Weaver, Pharm.D.,** and **Emily Woo, M.D., MPH** PHS officers nominated for companion award: **CDR Robert Ball, CAPT M. Miles Braun, LCDR Soju Chang, CDR John Quinn** and **CDR Joe Toning.**

Clinical Reviewers' Education Program Workgroup: **Mark Avigan, M.D., Karen**

(Continued on page 9)

CDER 2004 Report to the Nation now available in printed version

The Center's annual compilation of performance statistics, program descriptions and initiatives is available in a printed version. We have several hundred copies that we can mail out on a first-come, first-served basis.

If you are interested, please send an e-mail with a complete mailing address to dpapubs@cder.fda.gov.

You can find a Web-readable version of the report, a printable version and slides of the charts at:

- PDF—http://www.fda.gov/cder/reports/rtn/2004/rtn2004.pdf.
- HTML—http://www.fda.gov/cder/reports/rtn/2004/rtn2004.htm.
- Slides—http://www.fda.gov/cder/reports/rtn/2004/rtn2004.ppt.

CDER honor awards

(Continued from page 8)

Brugge, M.D., Wiley Chambers, M.D., Ann Farrell, M.D., Steven Gitterman, M.D., Ph.D., Jennifer Harris, M.D., Leonard Kapcala, M.D., Andrea Leonard-Segal, M.D., Jill Lindstrom, M.D., Markham Luke, M.D., Ph.D., Jack Morin, Jeffrey Murray, M.D., Anne Pariser, M.D., Philip Sheridan, M.D., Shari Targum, M.D. PHS officer nominated for companion award: **CAPT John V. Kelsey.**

Cluster ANDAs Review Team: **Richard Adams, Arup Basak, Ph.D., Rebacca Decker, Andrew Langowski, Susan Rosencrance, Ph.D., Shankar Saha, Ph.D., Nashed Samaan, Ph.D., Glen Smith, Ubrani Venkataram, Ph.D.,** and **Naiqi Ya, Ph.D.** PHS officers nominated for companion award: **LT Thomas Hinchliffe, LCDR Cuthbert Palat, III, LCDR David Skanchy** and **LCDR Stanley Shepperson.**

COOP Emergency Response Team: **Thomas Christl, Joan Flaherty** and **Robin Poole.** PHS officer nominated for companion award: **LCDR Michael Bourg.**

DPEIII Team: **Abimbola O. Adebowale, Ph.D., Chandra Chaurasia, Ph.D., Tapash Ghosh, Ph.D.,** and **Lei Zhang, Ph.D.**

Influenza Preparedness Team: **Debra Birnkrant, M.D., Edward Cox, M.D., MPH, Lorene Kimzey, Linda Lewis, M.D., George Lunn, Ph.D., Jeffrey O'Neill, Barbara Styrt, M.D., MPH,** and **Melissa Truffa, R.Ph.** PHS officers nominated for companion award: **CDR Valerie Jensen** and **LCDR Jouhayna Saliba.**

Methotrexate Drug Shortage Review Team: **Nallaperumal Chidambaram, Ph.D., Ramzi Dagher, M.D., Lorene Kimzey, Haripada Sarker, Ph,.D., John Simmons, Ph.D., Mike Verdi** and **Grant Williams, M.D.** PHS officers nominated for companion award: **CDR Valerie Jensen, LCDR Jouhayna Saliba** and **CAPT Paul Zimmerman.**

OGD Document Room Subcommittee: **Christopher Champagne, Gerrard Cuthbert, Eda Howard, Victoria Levi, Damaris Maldonado, Elizabeth McNeal, Hanh Nguyen, Jesus Orozco, William Rickman, Paul Schwartz, Ph.D., Lena Staunton, Marla K. Stevens-Riley, Ph.D., Linda Stone, Thomas Tokoli, Nadine Warren** and **Ruth Warzala.** PHS officers nominated for companion award: **LCDR James Barlow, LT Thomas Hinchliffe, LT Craig Kiester, CDR Steven Mazzella, LT Jeen Min** and **LCDR Martin Shimer.**

OGD Labeling Review Team: **Debra Catterson, R.Ph., Jacqueline Council, Pharm.D.,** and **Chan Park, Ph.D.** PHS officers nominated for companion award: **LCDR James Barlow, LCDR Postelle Birch, LCDR Michelle Dillahunt, LCDR Koung Lee, CDR Angela Payne, LCDR Malaine Shin, CAPT Adolph Vezza, LCDR Beverly Weitzman** and **LCDR Chi-Ann Wu.**

OPaSS Safety Support Group: **Charlene Flowers, R.Ph., Lopa Gohel, Pharm.D., Cindy Kortepeter, Pharm.D., Laurel Lee, Pharm.D., Susan Lu, R.Ph., Carol Pamer, R.Ph.,** and **Kate Phelan, R.Ph.** PHS officer nominated for companion award: **CDR Robert Pratt.**

Pediatric Suicidality Analysis Team: **Greg Dubtisky, M.D., Tarek Hammad, M.D., Alice Hughes, M.D., Thomas Laughren, M.D.,** and **Judith Racoosin, M.D., MPH** PHS officer nominated for companion award: **CDR Paul David.**

Radioactive Drug Research Committee: **Siham Biade, Ph.D., Young-Moon Choi, Ph.D., Jerry Collins, Ph.D., Sara Goldkin, M.D., Florence Houn, M.D., MPH, Christy John, Ph.D., Kyong Kang, Pharm.D., Adebayo Laniyonu, Ph.D., Eldon Leutzinger, Ph.D., Sally Loewke, M.D., George Mills, M.D., Lynn Panholzer, Pharm.D., Orhan Suleiman, Ph.D.,** and **Maria Walsh.** PHS officer nominated for companion award: **CAPT Richard Fejka.**

SPOTS Development Team: **Sheila Andrew, George Clanton, Maher Darwish, Dennis DelRosario, Charlene Do, Craig Eatmon, Michael Folkendt, Gary Gensinger, Gregory Hoover, Erika Jarvis, Amy Kaisler, Howard Kistler, Richard Lewis, Jiang Li, Weizhen Jane Lu, Maureen Moore, Matt Scholl, Arthur Shaw, Ph.D., Doug Stamper, Binh Ta, Sandra Valencia, Virginia Ventura, Obinna Ugwa** and **Jennifer Wagner.** PHS officer nominated for companion award: **LCDR Kellie Clelland.**

Stannsoporfin Working Group: **Suliman Al-Fayoumi, Ph.D., Ali Al-Hakim, Ph.D., Julie Beitz, M.D., Yash Chopra, Ph.D., Jasti Choudary, Ph.D., Japobrata Choudhury, Ph.D., Susan Cummins, M.D., MPH, Susan Daugherty, Suresh Doddapaneni, Ph.D., Julieann Dubeau, Eric Duffy, Ph.D., Sara Goldkind, M.D., Stella Grosser, Ph.D., Lawrence Grylack, M.D., Kenneth Hastings, DrPH, D.A.B.T., Robert Justice, M.D., Joyce Korvick, M.D., MPH, Paul Levine, Jr., R.Ph., Min Lu, M.D., MPH, Shirley Murphy, M.D., Densie Pica-Branco, Kathy Robie-Suh, M.D., Ph.D., Brian Strongin, R.Ph., Jean Wendy Temeck, M.D., Liang Zhou, Ph.D.** PHS officers nominated for companion award: **LT Monika Houston** and **CDR Lisa Mathis.**

Unapproved Prescription Drug Enforcement Team: **Herbert Gerstenzang, John Loh, Frederic Richman, Sakineh Walther** and **Valerie Whipp.** PHS officers nominated for companion award: **CDR Mark Askine** and **CDR William Russell.**

Jackie Barber Washington is the Center's incentive awards officer.

Biomarker imaging, laboratory study audits on topic list for retreat

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

The semi-annual scientific retreat for pharmacology and toxicology reviewers in the Office of New Drugs in March 2 focused on:

- Biomarker imaging in drug development.
- Nonclinical study audits and the inspection process.
- Guidance documents for safety testing of metabolites, genotoxic impurities and exploratory investigational new drug applications.
- A general update on accomplishments in the Office of New Drugs from its director, **John Jenkins, M.D.**

The retreat started with opening remarks from co-chairs **Haleh Saber-Mahloogi, Ph.D.,** and **John Leighton Ph.D., DABT. David Jacobson-Kram, Ph.D., DABT,** OND's associate director for pharm/tox, welcomed all to the meeting and got it underway.

Biomarker imaging

Biomarker imaging in drug development and licensed products. **George Mills, M.D.,** Director of the Division of Medical Imaging and Hematology Products, discussed biomarker imaging as it relates to:

- FDA's Critical Path Initiative.
- Current and translational biomarker imaging.
- The association between biomarker imaging and drug development.
- Successful biomarker development.
- Development of the draft guidance, *Exploratory IND Studies,* for biomarker imaging.

As the intent of the Critical Path Initiative is to improve and speed up drug development, FDA and the National Cancer Institute interagency imaging initiatives are being developed as well as other FDA collaborations in biomarker and PET imaging development. Current biomarker imaging includes pharmacokinetic studies with whole-body imaging for radiation dosimetry and organ biodistribution as well as targeting of select organs.

Translational biomarker whole-body imaging research provides opportunities to confirm preclinical assessments and to allow an enrichment of the early drug candidate selection process. Challenges for comparative biomarker whole-body imaging over multiple days include radiolabel selection, radiolabeling techniques and effective archiving of imaging results for current and future review and analysis. Safety issues are evaluated in current, successful biomarker imaging. Such issues include radiation injury risk to adjacent organs from radiation therapy exposure.

Imaging-based exploratory INDs, according to the draft guidance, would require limited preclinical development for proof-of-concept imaging because they expose subjects only to microdoses of the investigational drug. These studies could facilitate rapid portfolio assessment and result in an earlier separation of potential "winner and loser" investigational products. Issues still being addressed in the regulatory development of imaging biomarkers include whether imaging biomarkers should be a separate diagnostic IND or be developed within the investigational therapeutic agent's IND. The draft guidance is available at http://www.fda.gov/cder/guidance/6384dft.htm.

Good laboratory practice

Study audits and inspection process/compliance program. **C.T. Viswanathan, Ph.D.,** associate director of the Division of Scientific Investigations, provided an overview of CDER's good laboratory practice inspection program. These inspections support CDER's pharm/tox review process by verifying the nonclinical safety data.

Dr. Viswanathan highlighted the program's support of the decision-making process during the drug review with several case studies. These described the importance of:

- Determining the actual dose of the test article administered to study animals, specifically relating the ensuing toxicity or lack of it.
- Following the protocol, including all required elements in final reports.
- Selecting appropriate doses for genotoxicity testing.

The significance of test article characterization information and the results of dose formulation testing were discussed. Repeated violations of the regulations and non-compliance can lead to disqualification of a facility based on this program's risk-based management.

The study directors of nonclinical studies play a central role. While they can delegate technical responsibilities to other team members, they cannot delegate the overall responsibility for the conduct of the study.

Good laboratory practice requirements outside the United States were discussed, specifically those of the Organization for Economic Co-operation and Development. The OECD publication on the organization and management of multi-site studies was used to distinguish the test facility as the central unit and the multiple test sites with specialized expertise that conduct portions of GLP studies, as this is the current practice in many GLP studies. Effective communication between involved parties is essential and can eliminate potential problems in such studies.

Guidance updates

Safety Testing of Metabolites guidance. **Aisar Atrakchi, Ph.D.,** a pharmacologist in the Division of Psychiatry Products and co-chair of the Pharmacokinetic and Toxicokinetic Subcommittee of the Pharmacology and Toxicology Coordinating Committee, presented an overview of the draft guidance.

This draft document recommends the testing of "unique" human metabolites—those found only in humans—or "major" human metabolites—those found in disproportionately high levels in humans relative to the test animals. These metabolites may not be adequately tested in standard nonclinical studies because they did not occur or were present at very low levels in the animal species used during standard nonclinical toxicology evaluation.

The draft guidance addresses mainly metabolites detected in human plasma that represent greater than 10 percent of administered dose or systemic exposure,

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Draft guidance on metabolites explored through 2 case studies

(Continued from page 10)

whichever is less. Dr. Atrakchi discussed the general considerations on metabolite identification, study design, type of nonclinical studies required and timing of when to conduct these studies in relation to clinical development are discussed.

Genotoxic Impurities guidance. **Tim McGovern, Ph.D.,** a supervisory pharmacologist in the Division of Pulmonary and Allergy Products, discussed issues related to genotoxic impurities in drug substances and products. He included a review of relevant International Conference on Harmonization guidances and a recent proposal by the European Medicines Agency as well as an overview of recent experiences and practices regarding genotoxic impurities within the Office of New Drugs. In addition, he discussed some initial concepts included in a draft CDER guidance on this topic.

Exploratory INDs guidance. **Dave Green, Ph.D.**, the ODE I and Office of Antimicrobial Products associate director for Pharm/Tox, presented the exploratory IND as part of the Critical Path Initiative. This novel approach to INDs is intended to facilitate the identification of new approaches to the diagnosis and treatment of disease and specific, new drug candidates. Although minimizing the use of resources to identify risk, it maintains standards of patient safety that are consistent with traditional INDs. Three different examples of exploratory INDs were presented. The featured INDs demonstrated the application of the concept to the study of diagnostic imaging and pharmacokinetics, pharmacology and mechanisms of actions for drug and biologic products.

Case studies on metabolite guidance

Two case studies on the metabolite guidance were presented:

Tim Robison, Ph.D., DABT, from the Division of Pulmonary and Allergy Products, presented an example of a drug that is metabolized to form a unique human metabolite not found in significant levels in rodents.

This unique human metabolite was found to be positive in two genetic toxicity assays. In other words, the metabolite has a potential to damage DNA. There were concerns that rodent carcinogenicity studies with the parent drug would not assess the cancer-causing potential of the metabolite. Designs of rodent carcinogenicity studies with the isolated metabolite were discussed.

Fred Alavi, Ph.D., from the Division of Metabolism and Endocrinology Products, discussed toxicology issues related to a nitro degradant/impurity produced during wet granulation (0.3 percent) for which the sponsor wished to set a 1 percent manufacturing specification.

The structural activity relationship analysis found the degradant to be strongly positive for genotoxicity and carcinogenicity. The genotoxic potential of the degradant was confirmed by standard genotoxicity tests.

Because a human diet rich in nitrates and acidic stomach environment mimic the prerequisite conditions for nitro degradant formation, tests were performed to determine the nitro degradant concentrations in humans. It was discovered that approximately 10 percent of the parent drug was converted to nitro degradant *in vivo.*

Because the genotoxic degradant was produced at relatively high concentrations in humans, but not in rodents due to the differences in the diet nitrate content, carcinogenicity testing of the degradant was recommended.

OND updates and Q&A

John Jenkins, M.D., director of the Office of New Drugs noted that the office deserves congratulations for doing an outstanding job, and this is starting to be recognized by people outside of CDER.

A few additional full-time employees were added in fiscal year 2005, and they were assigned where the need was the greatest.

Drug safety communications. OND has had a primary focus on drug safety and will be looking at how it manages and communicates issues to the outside world. Some changes will deal with how we get external input, how we communicate with the public and how we interact with the Office of Drug Safety. While we had a public advisory committee meeting and followed those recommendations dealing with Vioxx, doctors and patients should have had better information about the cardiovascular risk information, Dr. Jenkins said. We will become more transparent in communicating and sharing post-approval drug risks. Information asymmetry is a new role for us, and we will become more proactive.

Process improvement. The guidance document dealing with Good Review Management Principles spells out the FDA's expectations for management of the review of new drug applications. While FDA is the gold standard for the world, that doesn't mean we can't improve on performance. We need to be more effective and efficient, because we can't control our workload. An independent consultant did an analysis and came up with recommendations for process improvement. We are now working on the transition during the reorganization and need to focus on 4 areas of process improvement (Meeting Management; Implementation of GRMPs; Post Marketing Safety Data and Post Approval Labeling Changes; and Updating of Processes and Procedures that feed into GRMPs)

Quality systems activities. Discussed previously, these principles (say what you do, do what you say, prove it, improve it), dovetail with GRMPs. We will continue to improve consistency and administration of activities, especially across divisions. Examples include, approaches for the large molecules that have been merged into CDER and guidances.

Retreat committee

The retreat was organized by pharm/tox reviewers and staff from various divisions at CDER including: **Siham Biade, Gary Bond, Luan Lee, John Leighton** (co-chair), **Haleh Saber-Mahloogi** (co-chair), **Yanli Ouyang, Tom Papoian, Tim Robison, Lilliam Rosario** and **Adele Seifried.**

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

CDER's small business workshop in Kansas City draws 125

BY RON WILSON

The Center and FDA's field operations co-sponsored a workshop in May in Kansas City for 125 representatives from the small pharmaceutical business community. The meeting provided small businesses with the opportunity to dialogue with subject matter experts from CDER and FDA's Office of Regulatory Affairs and gain an understanding of the regulatory requirements for approval and marketing of drug products. Regulatory compliance and other issues also were on the agenda.

This meeting was the second of its kind. Although the workshop was in the mid-West, attendees came from all parts of the country. We are working on holding a similar small pharmaceutical business workshop in Washington in the spring.

The topics and speakers were:

- *Introduction,* **John A. Friel,** deputy director, Office of Training and Communications.
- *Planning for successful, efficient, pharmaceutical product approval,* **Kim Colangelo,** associate director for regulatory affairs, Office of New Drugs.
- *Current challenges and concerns for generic abbreviated new drug applications,* **Martin Shimer,** branch chief, Regulatory Support Branch, Division of Labeling and Program Support, Office of Generic Drugs.
- *Regulatory aspects and challenges in the development of over-the- counter drugs,* **David Hilfiker,** supervisory project manager, Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products.
- *The basics of chemistry, manufacturing and controls,* **Ramnarayan Randad,** chemist, Division of Chemistry I, Office of Generic Drugs.
- *Top regulatory issues in the drug industry,* **John Thorsky,** ORA Kansas City district director.
- *Mastering regulatory compliance,* **Thomas Arista,** national expert, ORA Division of Field Investigations.
- *Federal financial incentives and assistance for small businesses,* myself.
- *The ORA small business representative program,* **David Arvelo,** ORA Southwest Region small business representative.

Ron Wilson is the director of CDER's small business assistance in OTCOM.

Pharmaceutical Inspectorate completes training for 23 field inspectors

BY PATRICK E. CLARKE

The Pharmaceutical Inspectorate training program graduated its first group of 23 field investigators in August. The program is a part of the strategic initiative to overhaul pharmaceutical regulatory and quality control systems (http://www.fda.gov/cder/gmp/).

"The program gives investigators more specialized, advanced training and the opportunity to interact with other regulatory and review offices within the Agency," said **Karen Hirshfield, R.Ph.,** a compliance officer in the Office of Compliance's Division of Manufacturing and Product Quality. Hirshfield is on the Pharmaceutical Inspectorate Course Advisory Group and the Level III Drug Investigator Certification Board.

The course advisory group—11 representatives from FDA's Office of Office of Regulatory Affairs, CDER and the Center for Veterinary Medicine—developed the curriculum. "Process analytical technology, facility design and statistics used at pharmaceutical manufacturing sites are just some of the areas covered in the last training module, technology," Hirshfield said.

The curriculum, which took more than a year to develop, included topics in:

- Risk management.
- Advanced quality systems.
- Current regulatory programs and procedures.
- Investigational techniques.
- Pharmaceutical science.

"It has been challenging to create the training program because it is brand-new and had to be developed from scratch," Hirshfield said.

Some of the criteria required for an investigator to go through the pharmaceutical inspectorate program include three years of experience in drug inspections and a Level II certification from ORA's Drug Investigator Certification Board.

The investigator must have district office approval and participate in a detail in either the Office of Compliance or the Office of Pharmaceutical Science. Many details are ongoing. "The details allow the investigators to be involved in the daily activities of the CDER offices in order to gain a better appreciation for what we do," Hirshfield said.

Three one-week training blocks are needed to complete the curriculum. The first block was held at the ORA University in August 2004. Compliance officers from CDER, ORA and CVM and reviewers from CDER and CVM participated in the training for a total of approximately 70 FDA employees.

"We're trying to foster interaction between investigators and compliance officers and chemistry reviewers," Hirshfield said.

The second week of training was held during the first week of February and the last training week was in August.

"The last week focused on technology, but we pulled together concepts taught in previous blocks," Hirshfield said. "For example, lessons in solid oral dosage form manufacturing also addressed how risk and quality principles apply."

Speakers for the courses have come from inside FDA, academia, industry and outside consulting firms.

"Some of the inside speakers have been top managers including **Janet Woodcock, M.D., David Horowitz** and **Helen Winkle** along with top ORA managers," Hirshfield said.

The goal agreed upon between CDER and ORA was that a total of 50 investigators will have completed the program by fiscal year 2007. Planning for selecting the next group of investigators and for the training course program is underway.

"The program is beneficial for investigators, reviewers and compliance officers," Hirshfield said, "and the interaction will streamline the process of putting inspectional information to the best use possible.