news along the pike

NOVEMBER 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

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PIKE'S CORNERS . . .

Research on DTC ads presented at public meeting

Influence of ads, ways to improve brief summary aired

BY AMIE BRAMAN, PH.D., AND KATHRYN AIKIN, PH.D.

The Center's Division of Drug Marketing, Advertising and Communications sponsored an FDA public meeting on direct-to-consumer advertising of prescription drugs on Sept. 22 and 23. The purpose was to hear from researchers who have investigated the promotion of prescription drugs directed to consumers through print, broadcast and other types of media.

FDA was especially interested in research on the impact of DTC advertising on the public health. During the two-day event, a panel of FDA staffers and members of the public listened to 29 presentations on issues such as the influence of DTC advertising on physician prescribing, the utilization and demand for DTC-advertised drugs, and ways to improve the communication of information in the "brief summary" of print advertising.

Firm conclusions from the public meeting cannot be made at this time because the docket remained open until Dec. 1. However, a few ideas emerged from the meeting:

- It appears from the research presented that there is no significant negative effect of DTC advertising, although areas of concern continue.
- DTC advertising seems to inform patients about available treatments and foster discussions between patients and physicians.
- Patients who ask about a specific drug are likely to be prescribed that drug.
- Patients do not comprehend the risks and

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FDA proposes incentive to remove illegal Rx drugs

By David J. Horowitz

FDA issued a draft guidance in October that describes how we intend to exercise our enforcement discretion regarding new drugs marketed without required FDA approval. Our policy provides an incentive for manufacturers to have these products meet modern standards. We estimate that there are several thousand illegally marketed drug products in the United States, comprising several hundred unique molecules.

These include some formulations of therapeutically important products such as morphine sulfate, hydromorphone, phenobarbital, barium sulfate, epinephrine, atropine sulfate and nitroglycerin sublingual.

When final, our proposal, titled *Marketed Unapproved Drugs—Compliance Policy Guide,* will:

- Clarify our interpretation of a complex area of drug law, regulation and policy that evolved over the last century.
- Specify a narrow reading of clauses in the

(Continued on page 10)

Dr. Galson promoted to rear admiral in Commissioned Corps

Acting Center Director **Steven K. Galson, M.D., MPH,** was promoted Nov. 1 to the rank of rear admiral in the Commissioned Corps of the Public Health Service. He is one of three officers promoted to that rank this year.

Dr. Galson joined CDER in May 2001 as deputy center director and has shared with the center director the executive direction of the CDER's scientific and regulatory activities. He also serves as the lead for several high-profile FDA and HHS initiatives such as patient safety.

He came to the Center with a background in emerging health and science issues and regulatory reform at the Environmental Protection Agency, the Department of Energy and the National Institute of Occupational Safety and Health.

Dr. Galson received his medical degree from the Mount Sinai School of Medicine in New York. He earned his master's in public health from Harvard University. He entered the Commissioned Corps in 1986 with the Centers for Disease Control and Prevention.

JOE'S NOTEBOOK

Reflections on World Diabetes Day

World Diabetes Day, which was Nov. 14, may have passed below most our radar screens, but odds are it affects someone close to you—a relative, friend, neighbor or co-worker. Watching the progression of the disease in a neighbor has been hearth-wrenching for me and my family.

HHS used the occasion of World Diabetes Day to announce that, sadly, the number of Americans with diabetes rose to an all-time high. In 2003, an estimated 18.2 million fellow citizens—that's 6.3 percent of us—have diabetes.

The new diabetes estimates are based on data from the Centers for Disease Control and Prevention, the National Institutes of Health and the Indian Health Service. Highlights of the updated data include:

- Diabetes continues to be the nation's sixth leading cause of death.
- An estimated 13 million Americans have been diagnosed with this disease, and about 5.2 million more Americans have the disease but have not been diagnosed.
- Diabetes is the leading cause of blindness among adults between 20 and 74 years old.
- 14.9 percent of American Indians and Alaska Natives who are at least 20 years old and receive care from IHS have diabetes. American Indians and Alaska Natives are 2.3 times more likely to have diabetes than non-Hispanic whites of similar age.
- 11.4 percent of non-Hispanic blacks 20 years old or older have diabetes. On average, non-Hispanic blacks are 1.6 times more likely to have diabetes than non-Hispanic whites of a similar age.
- 8.4 percent of non-Hispanic whites 20 years old or older have diabetes.
- 8.2 percent of Hispanics 20 years old or older have diabetes. On average, Hispanic Americans are 1.5 times more likely to have diabetes than non-Hispanic whites of similar age.
- Native Hawaiians and Japanese and Filipino residents of Hawaii 20 years old or older are twice as likely to have diabetes as white residents of Hawaii.

The data are included in a new HHS 2003 National Diabetes Fact Sheet available at http://www.cdc.gov/diabetes/pubs/factsheet.htm. The fact sheet defines diabetes, describes treatments, identifies "prediabetes" (a term used to describe people at increased risk of developing diabetes), and briefly discusses the control of glucose, blood pressure, blood lipids and preventive care practices for the eyes, kidneys and feet.

Diabetes is a group of diseases characterized by high levels of blood glucose resulting from defects in the body's insulin production, insulin action or both. Serious complications and premature death are associated with diabetes, but people with diabetes can take steps to control their disease and lower the risk of complications.

"Prevention is the key to stemming this unfolding epidemic," CDC Director **Julie Gerberding, M.D.,** said. "By eating a healthy diet and engaging in regular physical activity, individuals can greatly reduce their risk of developing type 2 diabetes."

Modern medicine is also helping people control the disease. Among adults with diagnosed diabetes, 12 percent take both insulin and oral drugs, 19 percent take insulin only, 53 percent take oral drugs only and 15 percent take neither insulin nor oral drugs.

Many Americans are unaware that they may be at risk for—or already have—diabetes. Early diagnosis and proper treatment of diabetes can delay, and even prevent, the progression of serious health problems such as heart disease and stroke, blindness, lower limb amputations and kidney failure.

news along the pike

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CDER medical officer, Reservist makes a difference in Afghanistan

By Patrick E. Clarke

David Gan, M.D., DrPH, MPH, a medical officer in the Division of Scientific Investigations in the Office of Medical Policy, is testimony to the fact that one person—under the right circumstances—can bring about change.

"I never thought I would be in a position where I was actually influencing the health policies of a country," said Dr. Gan, a major in the Army Reserve. He recently returned from a year-long tour of duty in Afghanistan, where he served as the medical director of the Coalition Joint Civil Military Operations Task Force. He was the only HHS official in the country and the only American doctor tasked to work with the Afghan government and other international agencies to reconstruct the country's health care system. Dr. Gan was awarded the Bronze Star for outstanding service for his efforts there.

Dr. Gan holds both master's and doctorate degrees in public health with a specialization in epidemiology from Tulane University in New Orleans. With both his practical and educational experience, Dr. Gan was involved in formulating major health care policy for Afghanistan. "You must develop a very good working relationship with people or you can't help them influence policy," Dr. Gan said.

He had to cut through red tape and coordinate with both internal and external organizations.

Dr. Gan had only been working for CDER for 15 months when he got his deployment orders. "I knew the deployment was coming and could have gotten out of the Reserve, but I wanted to serve my country," Dr. Gan said.

His deployment began with one month of mobilization training at Fort Bragg, N.C. In addition to physical, chemical warfare and weapons training, he had classes on topics such as the Afghan culture and language. "Plus, I was the battalion surgeon, so I had to make sure there were medical supplies for everyone," Dr. Gan said. Once in Afghanistan, Dr. Gan worked 12-hour days every day with no time off. The need was there.

In Afghanistan, Dr. Gan was appointed as the principal coordinator for the Department of Defense and HHS efforts to establish maternal and child health projects in Afghanistan.

Currently, 40 percent of deaths among women of childbearing age in Afghanistan are caused by preventable complications related to childbirth. The child mortality rate in Afghanistan is the worst in the world. "Before a child there reaches the age of 5, every fourth child will die," Dr. Gan said.

In addition to helping coordinate various U.S. initiatives, Dr. Gan was asked by the Afghan ministers of health and foreign affairs to help reconstruct the Afghan pharmaceutical industry. The Operations Task Force renovated the government-owned pharmaceutical company, as Dr. Gan worked with the Afghan minister of health to privatize the company.

Dr. Gan also led the effort to help resume production at a pharmaceutical plant owned by a German company that didn't want to return. Working with the ministers of health and foreign affairs, among others, Dr. Gan got a commitment from another pharmaceutical company to invest $20 million and reopen the site.

One of the key policies he helped institute was moving the Afghan healthcare system to more of a cost-recovery model. "Doctors in Afghanistan only make $50 a month. They've had kind of a socialist system," Dr. Gan said. "We started a pilot study involving cost recovery—charging just a small amount such as 5 cents a patient." Eventually, pilot cost-recovery programs were installed in over 30 clinics throughout Afghanistan. "As a result of the cost-recovery practices, the clinics provide better quality health care to patients," Dr. Gan said.

He's been told to expect a letter of appreciation from Afghan President Harmid Karzai. He was presented with a certificate of appreciation from the Afghanistan Minister of Health that states in part: "You have made great contributions to reconstruct the healthcare system in Afghanistan." Dr. Gan was also pleasantly surprised to find that "99 percent of the people there like us because they've just been through 23 years of war." Dr. Gan spent hundreds of dollars of his own money buying items for patients.

Although the majority of people liked Americans, it was still a dangerous area. "Anywhere outside of our compound you had to go as a team, with your weapons loaded and ready to fire," Dr. Gan said. "There really was no protection—if someone wants to kill you, they will. I prayed a lot." He recalled a group of German soldiers and medical personnel who were attacked by a suicide bomber on the day they were scheduled to leave the country. Four of the group were killed. "I was very careful during my last month there," Dr. Gan said.

One of the worst pressures Dr. Gan had to face was concern for his family. "My wife is very religious, and she got great support from our local church," Dr. Gan said. His son turned 17 while he was gone, and Dr. Gan worried about not being home while his son was applying to various colleges. "But, my son won about $75,000 in scholarship money from Westinghouse, the Army and other organizations and is going to Harvard, so he did OK without me," Dr. Gan said proudly. "My daughter, who is 13 now, may have missed me the most. We used to jog together every day. I know they prayed for me every day."

Dr. Gan is appreciative of how CDER helped him. "Dr. Woodcock e-mailed me several times, and I received hundreds of e-mails from CDER employees," Dr. Gan said. "Especially at holidays, the e-mails made my day. I read every single one and tried to reply to them all."

He's also grateful to three people in his section who stepped in and performed his job responsibilities while he was gone. "**Dr. Khin U, Carolanne Currier,** a consumer safety officer, and **Michele Lackner,** a consumer safety technician, really made sure my duties were accomplished in an exemplary manner," Dr. Gan said.

Dr. Gan has been asked by HHS Secretary **Tommy Thompson** and FDA Commissioner **Mark McClellan, M.D., Ph.D.,** to go back periodically to Afghanistan as a civilian to continue to help accomplish some of the department's initiatives. Meanwhile, he is just grateful to have made it back. "I appreciate our life here in America so much more now," Dr. Gan said. "The experience changed me. I want a simple life now."

CDER volunteer faculty for academic year 2002-2003 recognized

By Chris Nguyen and Jack Morin

CDER's volunteer faculty provides invaluable services. These dedicated volunteers share their time, knowledge and experience with their colleagues. The Center's volunteer faculty number more than 200, and they research, plan, develop and deliver courses without additional compensation in addition to their regular work.

The Division of Training and Development in the Office of Training and Communications recognizes the hard work and dedication of the following volunteer faculty during the 2002-2003 academic year. The course and faculty were:

An Introduction to the Center for Drug Evaluation and Research: **Susan Allen, M.D., MPH, Joan Blair, Debra Boxwell, Igor Cerny, Pharm.D., Antoine El-Hage, Ph.D., John Friel, J.D., Kathleen Frost, Roger Goetsch, Pharm.D., David Graham, M.D., MPH, Roger Gregorio, Brian Hasselbach, Deborah Henderson, R.N., MSN, David Hilfiker, M.S., Carol Holquist, R.Ph., Carolyn Hommel, John Jenkins, M.D., Jean-Ah Kang, David Konigstein, R.Ph., Sandra Kweder, M.D., Denis Mackey, Norman Marks, M.D., Andrea Masciale, Esq., Justina Molzon, M.S., Pharm.D., Barry Poole, R.Ph., Terri Rumble, BSN, R.N., Ellen Shapiro, Ted Sherwood, John Simmons, Ph.D., Nancy Smith, Ph.D., Karen Templeton-Somers, C.T. Vishwanathan, Leslie Wheelock, M.S., R.N., Sally Winthrop** and **Janet Woodcock, M.D.**

Basic Statistical Methods: **Ruthie Davi, M.S., Karen Higgins, Sc.D., Kate Meaker, M.S.,** and **Dionne Price, Ph.D.**

New Reviewers' Workshop: **Fred Alavi, M.S., Ph.D., Aisar Atrakchi, Ph.D., Sammie Beam, Magdalene Carolan, M.S., MSLS, Igor Cerny, Pharm.D., Chris Cole, James Cross, Susan Cruzan, Ruthie Davi, M.S., Gregg Davis, R.Ph., Jennifer DiGiacinto, Antoine El-Hage, Ph.D., Amy Ellis, Ph.D., Harvey Greenberg, Joe Hanig, Ph.D., Mark Hirsch, M.D., Dena Hixon, M.D., Elaine Hu, R.Ph., Stephen Langille, Randy Levin, M.D., Tim Mahoney, Sheldon Markofsky, Ph.D., Frederic Marsik, Ph.D., ABMM, Iris Masucci, Melissa Maust, Kathie McConnell, Kate Meaker, M.S., Joette Meyer, Pharm.D., Catherine Miller, Judit Milstein, James Morrison, Armando Oliva, M.D., Jacqueline O'Shaughnessy, Lana Pauls, MPH, Marilyn Pitts, Kathleen Quinn, Jerry Rachanow, P.D., J.D., Terri Rumble, BSN, R.N., Warren Rumble, John Senior, M.D., Martin Shimer, Lisa Stockbridge, Ph.D., Mike Verdi** and **Sarah Singer.**

390 Retreat: **Renata Albrecht, M.D., Robin Anderson, R.N., MBA, Shukal Bala, Ph.D., Sary Beidas, M.D., Ellen Frank, R.Ph., Steven Gitterman, M.D., Rita Hecker, Steve Kunder, Ph.D., Kristen Miller, Pharm.D., Rigoberto Roca, M.D.,** and **Diana Willard.**

CASE 2002-2003: **Hamid Amouzadeh, Ph.D., Aisar Atrakchi, Ph.D., Shukal Bala, Ph.D., Narayana Battula, Ph.D., Lucinda Buhse, Ph.D., Mamta Gautam-Basak, Ph.D., Hanan Ghantous, Ph.D., Gurpreet Gill-Sangha, Ph.D., Karen Higgins, Sc.D., Len Kapcala, M.D., Markham Luke, M.D., Ph.D., Joette Meyer, Pharm.D., Patrick Nwakama, Pharm.D., John Quinn, R.Ph., M.S., William Rodriquez, M.D., Ph.D., Curtis Rosebraugh, M.D., MPH, Arzu Selen, Ph.D., Philip Sheridan, M.D., Milton Sloan, Ph.D., Rajeshwari Sridhara, Ph.D., Saleh Turujman, Ph.D.,** and **Sue Jang Wang, Ph.D.**

Videoconference Focal Points: **James Angel, James Black, Lisa Gilmer, Ayse Hisim, M.S., Merla Matheny, Jamie Metz, Jody Moore, Paul Neff, Laura Riddle, Joyce Routh, Ruth Warzala, Kristen West** and **Donnie Wisner.**

Liposomes—Scientific and Regulatory Challenges: **Aisar Atrakchi, Ph.D., Brian Booth, Ph.D., Mei-Ling Chen, M.D., Mamta Gautam-Basak, Ph.D., Gene Holbert, Ph.D., Kofi Kumi, R.Ph., Ph.D., Jeffrey Murray, M.D., MPH, Eileen Navarro-Almario, M.D., Nam Atigur Rahman, Ph.D., Arzu Selen, Ph.D., Grant Williams, M.D.,** and **Lianh Zhou, Ph.D.**

New Employee Orientation: **Laura Bradbard, Magdalene Carolan, M.S., MSLS, Roy Castle, Heather Chafin, Nichelle Cherry, MSLS, Lois Chester, MLS, Davis Hilfiker, M.S., Michael Jones, Karen Kapust, MLS, Lana Kostecka, Kathy Kruse, MLS, Andrea Masciale, Esq., Judit Milstein, Wayne Mitchell, Esq., Crystal Rice, Terri Rumble, BSN, R.N., Ellen Shapiro, Ted Sherwood, John Simmons, Ph.D., Michael Theodorakis, Kathleen Quinn, Mitch Weitzman, Sally Winthrop** and **Robert Young, M.D.**

Advisory Committee Meetings Workshop: **Igor Cerny, Pharm.D., Heather Chafin, Gemma Kuijpers, Ph.D., Marianne Mann, M.D., Andrea Masciale, Esq., Joy Mele, M.S., Thomas Permutt, Ph.D., Kathleen Reedy, RDH, M.S., Kimberly Topper, M.S.,** and **John Treacy.**

NDA Regulations and Policies: **Barbara Chong, Bronwyn Collier, BSN, Julieann DuBeau, R.N., MSN, Michael Folkendt, Ellen Frank, R.Ph., Melodi McNeil, R.Ph., M.S., David Roeder, M.S., James Rogers, Robbin Nightswander, R.Ph., M.S., Marianne Mann, M.D.,** and **Terri Rumble, BSN, R.N.**

Successful Meetings and Minutes: **Christy Cottrell, Patrick Guinn, Alice Kacuba, Deborah Kallgren, Judit Milstein, Raquel Peat** and **Maureen Pelosi.**

IND Regulations and Policies: **Nancy Derr, Jackie Ware** and **Cathie Schumaker.**

Topics in Clinical Trials: **Susan Ellenberg, Ph.D., Robert Temple, M.D.,** and **Judy Racoosin, M.D., MPH**

University of North Carolina Physician Fellows Visit with CDER: **Kathleen Frost, Susan Honig, M.D., Melodi McNeil, R.Ph.,** and **Robert O'Neill, Ph.D.**

Tools for Pre-Approval Drug Safety Evaluation: **Steve Gitterman, M.D., Shiew-Mei Huang, Ph.D., Lawrence Lesko, Ph.D., Zilli Li, M.D., Robert O'Neill, Ph.D., Judith Racoosin, M.D., MPH, Victor Raczkowski, M.D., John Senior, M.D., Lee Simon, M.D.,** and **Douglas Throckmorton, M.D.**

(Continued on page 5)

TRAINING AND DEVELOPMENT CORNER

Clinical update seminars bring latest developments to reviewers

BY DALE WILCOX AND JACK MORIN

The Clinical Reviewers Education Program is an ongoing, monthly series of three-hour seminars designed to help clinical reviewers keep up-to-date with the latest developments in medical specialties and subspecialties other than their own. Each clinical update seminar has a maximum of three hours of Category 1 continuing medical education credit.

For autumn 2003, two seminars have been completed and one remains. The medical specialty covered, the dates and the CDER faculty coordinator are:

- *Cardiology,* Sept. 10, **Shari Targum, M.D.**
- *Dentistry,* Oct. 16, **John V. "Jake" Kelsey, DDS, MBA.**
- *Rheumatology,* Dec. 5, **Andrea Leonard Segal, M.D.**

Seventy-one FDA staff attended the cardiology update. The guest speakers, all eminent cardiologists, spoke on a variety of subjects including interventional cardiology, the evolution of drug evaluation, atrial fibrillation, non-pharmacologic treatment of arrhythmias and acute coronary syndrome.

For next year, the medical specialties or topics selected for updates so far, the month tentatively scheduled and the CDER faculty coordinators are:

- *Gastroenterology,* January, **Mark Avigan, M.D.**
- *HIV,* February, **Jeffrey Murray, M.D., MPH.**
- *Oncology,* March, **Ann Farrell, M.D.**
- *Dermatology,* April, **Jill Lindstrom, M.D.**
- *Psychiatry,* May, **Karen Brugge, M.D.**
- *Hematology,* June, Dr. Farrell.
- *Ophthalmology,* September, **Wiley Chambers, M.D.** and **Jennifer Harris, M.D.**

These three-hour seminars were developed to meet a need that clinical reviewers identified during their first retreat held in November 2001. A working group was formed to plan and develop a series of clinical updates. The group included **Leonard Kapcala, M.D., Markham Luke, M.D., Ph.D., Anne Pariser, M.D.,** and Dr. Segal from the Office of New Drugs and **Dale F. Wilcox** from the Office of Training and Communications.

A survey was sent to all CDER clinical reviewers to assess how best to meet this need. As a result of this survey, the Division of Training and Development worked with the clinical review staff to develop and deliver pilot seminars on neurology and endocrinology for fall 2002. These two seminars received favorable comments from the Center's clinical reviewers.

Subsequently, the Clinical Reviewer Education Program Workgroup was formed to identify appropriate scientific topics, identify guest speakers and serve as CDER faculty coordinators for these seminars.

In addition to the physicians already mentioned, the group also includes **Steven Gitterman, M.D.** and **Philip Sheridan, M.D.**

Please register online for the seminars on DTD's CDERnet site at http://cdernet.cder.fda.gov/dtd/index.htm. Your registration helps us plan for sufficient chairs, handouts and an adequately sized conference room. E-mail either of us if you have questions.

Dale Wilcox is a supervisory training specialist in DTD, and Jack Morin is a writer and editor in DTD.

Volunteer faculty

(Continued from page 4)

Toxicologic Pathology II: **Elizabeth Hausner, DVM.**

Evaluating Human Pregnancy Outcome Data: **Dianne Kennedy, R.Ph., MPH, David Morse, Ph.D.,** and **Sandra Kweder, M.D.**

Survival Data Analysis: **Kate Meaker, M.S.**

Videoconferencing Skills Course: **Pamela Winbourne.**

Clinical update seminars

Endocrinology Update: **Theresa Kehoe, M.D., Robert Perlstein, M.D.,** and **Anne Pariser, M.D.**

Neurology Update: **Leonard Kapcala, M.D.**

Chris Nguyen is a training specialist in DTD and Jack Morin is a writer and editor in DTD.

IOM elects McClellan, Crawford as members

The Institute of Medicine announced its election of **Mark B. McClellan, M.D., Ph.D.,** and **Lester M. Crawford, DVM, Ph.D.,** respectively the FDA's commissioner and deputy commissioner, as members of the institute.

The IOM is a leading organization that advises the government on the most critical issues in medicine and public health.

The institute is a non-profit component of the National Academies of Sciences.

It has elected individual FDA scientists in the past, but never both the commissioner and the deputy commissioner.

New IOM members are chosen worldwide on the basis of their distinguished professional achievement in a field related to medicine and health, and on their involvement in health care, disease prevention, education and research.

CDER, SAMHSA share communications award

The public education campaign on the misuse of prescription pain relievers (http://www.fda.gov/cder/pike/JanFeb2003.htm#Abuse) sponsored by CDER and the Substance Abuse and Mental Health Services Administration won a communications award.

The Paul G. Rogers 2003 Medication Communicator Award will be presented to the HHS agencies by the National Council on Patient Information and Education at its national conference to be held Dec. 9.

NCPIE is a diverse nonprofit coalition of organizations committed to safer, more effective medicine use through better communication. **Ayse Hisim,** a public affairs specialist in the Office of Training and Communications, is the CDER project manger for the campaign.

BIOLOGICS CORNER

For biologics reviewers, process defines the product

BY KAREN WEISS, M.D.

On Oct. 1, the clinical and preclinical review staff and the project management staff for therapeutic biologicals became official members of CDER's Office of Drug Evaluation VI, a part of the Office of New Drugs.

While the review of clinical safety and efficacy is very similar for drugs and therapeutic biologicals, fundamental differences exist between drugs and biologicals. The classic dichotomy can be seen in the product labels. For a small-molecule drug, a diagram depicting the chemical structure usually appears in the description section. That type of diagram is almost never present in labels of biological products, which tend to be large and complex proteins that do not readily lend themselves to diagrams.

"Traditional" biologicals were poorly characterized proteins. It was not possible to characterize all the components of a biological product sufficiently to make a generic version. In fact, it was also difficult for the same manufacturer to characterize its own product sufficiently to ensure lot-to-lot consistency.

One way to minimize this problem was to institute a system of controls over all aspects of the manufacturing process (in-process controls). The old saying in biologics was: "The process defines the product." Process changes could introduce changes to the molecule that might not be detected by standard chemical and molecular biology characterization techniques, yet could profoundly alter the safety or efficacy profile.

There is more blurring of the lines between drugs and some of the newer recombinant proteins. These biotech products tend to be purer and better characterized than traditional biologics. In addition, there has been a lot of progress in analytical tools. Manufacturers can usually introduce changes to improve aspects of the product or its yield, and show the new product is the "same" as the older product by analytical tests, rather than by generating extensive clinical efficacy data.

Many therapeutic biologicals are recombinant versions of endogenous proteins. Despite their similarities to naturally occurring substances, the body may consider them "foreign" proteins and an immune response can occur in the recipient.

An important part of the review of any therapeutic biological is evaluation of the immunogenicity data. This is a multidisciplinary approach—product experts evaluate the sensitivity and specificity of the assay itself and the characterization of the immune responses, such as whether they neutralize the activity of the product. Clinical reviewers must consider whether immune responses alter the serum levels of the product, affect clinical safety and efficacy or both.

"Process changes could introduce changes to the molecule that might not be detected by standard chemical and molecular biology characterization techniques, yet could profoundly alter the safety or efficacy profile."

Pre-clinical safety assessments of the therapeutic biologicals can be challenging. Many recombinant proteins are species specific. Toxicology studies in small animals such as rodents may not be relevant to humans. Also, animals may rapidly develop an immune response to a recombinant human protein product, which has implications for the ability to conduct chronic toxicity studies.

Another large difference between drugs and biologicals is the starting, or source, material. Biologicals are derived from living sources, including cells, organs and tissues. There is the potential for a biological product to be contaminated with adventitious agents, despite vigorous manufacturing steps designed to inactive or eliminate such contaminants, should they be present. Consent forms and product labels indicate this possibility.

While the majority of drugs have orally administered dosage forms, the majority of therapeutic biologicals are broken down in the digestive system and, therefore, must be parenterally administered, such as by intravenous or intramuscular injection. The exceptions are a few topical products. Thus, we do not have multiple dosage forms for biologicals, such as capsules, tablets, patches and so on.

Some of the more frequently asked questions that we have received from industry since we consolidated with CDER are:

- *Will previous commitments between FDA and industry be honored?* Yes, unless new scientific evidence causes need for change. Remember, for the most part, our reviewers for specific products are not changing.
- *Will Biological License Applications going to CDER become NDAs; will new biotech products be NDAs?* No. The law defines the regulatory mechanism for biologics. There is no plan to convert existing BLAs to NDAs. Furthermore, there is no plan to initiate an NDA mechanism for new biologic products.
- *Will requirements for facilities and equipment remain the same?* Yes, because the risks remain the same. However, there will be a reassessment of need for reporting under the FDA initiative: Pharmaceutical cGMPS for the 21st Century (July 2002 *Pike*).
- *Will bi-annual inspections (Team Biologics) remain the same?* Yes, for now. There will be a re-evaluation under the cGMP initiative
- *Will there be generic biologicals?* The legislative history appears silent on whether a regulatory scheme similar to that for generic drugs could be applied to biologics. Biologics are licensed under the PHS Act, which lacks provisions similar to those in the FD&C Act for generic drugs. Also, the Hatch-Waxman Act doesn't apply to biologics. We are exploring ways that a product comparable to a well-characterized off-patent biologic could be brought to market without unnecessary clinical investigations.

When we consolidated with CDER, we brought with us 54 approved BLAs and about 1,500 INDs. ODE VI has three

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PEDIATRICS CORNER

Pediatric Research Equity Act of 2003 passed by Congress

Congress passed the Pediatric Research Equity Act of 2003 on Nov. 19. This legislation, when signed into law, will provide FDA with authority to require pediatric studies of pharmaceutical products when such studies are needed to ensure the safe and effective use of the products in children.

"The public health of children will be best served by enabling FDA to require testing of drugs for pediatric use, when drug firms do not test them voluntarily," said HHS Secretary **Tommy G. Thompson** and FDA Commissioner **Mark B. McClellan, M.D., Ph.D.,** in a written statement.

For pharmaceutical companies that conduct FDA-requested testing of drugs with existing patents or marketing exclusivity, the Best Pharmaceuticals for Children Act, which was signed into law in January 2002, allows FDA to extend marketing exclusivity. This incentive has resulted in a significant increase in the number of pediatric studies performed and in important information to guide safer and more effective use of medicines in children. So far, 91 medicines have had studies completed.

In 1998, FDA had promulgated a final regulation known as the Pediatric Rule in order to help assure that those products that did not benefit from the exclusivity incentive also had needed pediatric studies performed. However, in October 2002, the U.S. District Court for the District of Columbia held that FDA lacked sufficient statutory authority to require pediatric studies and prevented FDA from enforcing the requirements.

Instead of pursuing a time-consuming appeal of the ruling, HHS called on Congress to work with the department to write legislation that would provide FDA with the authority to require pediatric studies.

"We thank the members of Congress for their determined efforts to secure enactment of legislation to authorize FDA to require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials," Thompson and Dr. McClellan said. "We look forward to the president signing this legislation into law."

A copy of the legislation can by found by typing the bill number, S.650, into a THOMAS search on the Library of Congress' Web site at http://thomas.loc.gov/.

INFORMATION TECHNOLOGY CORNER

New version meeting tracking system on tap; network upgrades

BY LINDA SIGG, BINH TA AND COLLEEN RATLIFFE

The new version of the Industry Meeting Tracking System will be available for use starting in December.

The Industry Meeting Tracking System supports the tracking of scheduled meetings between Agency personnel and the drug industry. IMTS allows CDER management to monitor performance against Prescription Drug User Fee Act goals for industry-requested meetings and to track meeting workload.

In addition, the tracking system supports tracking information for meetings that FDA requests with external constituents and also within FDA internal organizations.

The new tracking system will provide users with:

- A Web-based interface.
- Data entry automation.
- Integration with DFS to display meeting minutes.
- Better reporting functionality via the Business Objects reporting tool and other functional enhancements for tracking meetings, such as data downloads to Microsoft Excel.

These enhancements will give CDER staff the tools needed to better manage and meet performance goals as required by PDUFA III.

Announcements for training sessions will be sent out soon.

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

10 Net conversions

BY FRED GOETZE

After some initial delays, OIT will be updating all of the CDER building locations to a newer IP address that will provide communication for all PCs, printers and all other network equipment. We are performing the necessary changes during non-maintenance weekends and some federal holidays during November and December.

As a result, all systems and applications, including e-mail in these buildings will be unavailable during the work time. A message for each of the building locations to be changed will be sent out with about a week's notice.

Fred Goetze is a acting director of OIT's Division of Infrastructure Management and Services.

For biologics reviewers in new ODE VI, process defines the product

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divisions. Our medical and pharmacology/toxicology reviewers are either in the Division of Therapeutic Biological Oncology Products or the Division of Therapeutic Biological Internal Medicine Products. Our project managers are in the Division of Review Management and Policy (last Pike).

The therapeutic biological products now under CDER's review include:

- Monoclonal antibodies for *in-vivo* use.
- Cytokines, growth factors, enzymes, immunomodulators and thrombolytics.
- Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors).
- Other non-vaccine therapeutic immunotherapies.

More information about biological therapeutic products, including how to contact us, can be found on CDER's Web site at http://www.fda.gov/cder/biologics/default.htm.

Karen Weiss is the director of ODE VI.

DTC ad research presented at meeting shows little negative effect

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benefits in DTC advertisements equally well.

- The brief summary in print advertisements merits reevaluation. FDA is considering ways to address this last concern.

Although DTC advertising was never prohibited, its volume increased dramatically after the issuance of FDA's draft 1997 guidance clarifying how companies may advertise prescription drugs on television and other broadcast media without including detailed prescribing information. The elements of the guidance, finalized in 1999, are summarized in a previous issue of *News Along the Pike* (see "More Understandable TV Ads of Rx Drugs on Way," August 27, 1997, pp. 1, 11).

At the time the guidance was issued, FDA reiterated its plan to evaluate the effects of this guidance on the public health. The recent public meeting, along with FDA's own research on the topic, is part of that evaluation.

Due in no small part to its high visibility, FDA has received pressure on all sides regarding this issue. Although FDA welcomes the input of various perspectives, the Agency feels that empirical evidence is the best way to investigate whether DTC advertising has positive effects, negative effects or both. FDA will consider the research to explore whether its current regulatory approach should be modified and, if so, how. Thus, the focus of the public meeting was on information-seeking and not on policy decisions.

Presenters were organized by topic into seven panels. Each speaker was allotted 15 minutes for his or her presentation. The presenters on each panel then collectively answered questions from the FDA panel, which included representatives from DDMAC, the Office of the Commissioner, Office of External Relations, Office of the Chief Counsel, Office of Medical Policy, the Center for Veterinary Medicine, the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health. Pending time constraints, audience members asked questions as well.

The meeting began with an introduction by **Thomas Abrams, R.Ph., MBA,** director of DDMAC, remarks by **Janet Woodcock, M.D.,** CDER director and a report of FDA research by one of us (Kathryn Aikin). FDA presented the results of its three surveys—two with patients and one with physicians—on the impact of DTC advertising on the doctor-patient relationship. Results of the physician survey are summarized in a previous issue of *News Along the Pike* ("FDA's physician survey on DTC Rx drug ads shows health benefits," Feb. 21, 2003, p. 5).

The results of these surveys indicate the impact of DTC advertising may be somewhat mixed. In the opinion of both patients and physicians, DTC advertising is very good at increasing awareness of potential treatments and helps doctors and patients have better discussions. Approximately 18 percent of patients reported that a DTC ad had caused them to talk to a doctor about a medical condition they had not previously discussed.

More physicians report beneficial effects vs. detrimental effects from their patient's viewing of a DTC advertisement. However, physicians feel these ads do not convey information about the risks and benefits of the product equally well. They believe their patients understand the benefits much better than the risks.

General practitioners report feeling more pressured to prescribe compared to specialists. Finally, physicians are evenly divided in opinions about the overall impact of DTC ads on their patients and practice—about one-third believe it has a positive effect, one-third believe it has a negative effect, and one-third believe it has had no effect at all. More details about these three surveys can be found online at http://www.fda.gov/cder/ddmac/presentations.htm.

Following the FDA presentation, researchers representing diverse interests presented their findings. Thomas Abrams moderated the first day's three panels and **Melissa Moncavage, MPH.,** DTC review group leader in DDMAC, moderated the second day's four panels.

The majority of presenters were affiliated with academia, including representatives from Columbia, Duke, Dartmouth, and Harvard universities and the Universities of British Columbia, California, Michigan, Minnesota and Texas.

Several representatives from the pharmaceutical industry also participated, including representatives from Pfizer Inc., Pharmaceutical Research and Manufacturers of America and the Patient Marketing Group Inc.

A number of consumer groups were also represented, including the National Consumers League.

Presenters covered a range of topics concerning DTC advertising. Basic issues discussed included:

- Results of national surveys of attitudes and health effects.
- Effects of DTC advertising on prescribing behavior.
- DTC advertising effectiveness.
- Utilization and demand for DTC-advertised drugs.
- Usage and improvements of the brief summary in DTC print advertisements
- Patient/physician interactions around the world.
- DTC advertising effects on patient compliance.

Much of the research presented was consistent with the findings of the FDA patient surveys of 1999 and 2002. For example, Ed Slaughter of Rodale Inc., the publishers of *Prevention* magazine, presented the results of six years of survey data. His results reveal that 78 percent of respondents believe that DTC advertisements allow people to become more involved in their health care and that approximately one-third of the respondents talked to a doctor as a result of DTC advertising exposure.

Julie Donohue of Harvard Medical School and others reported that DTC advertising is only a small factor in determining health outcomes when compared with other factors. For instance, while DTC advertising had no discernable effect on choice of antidepressant medication, the practice of detailing in physicians' offices had a large effect. The FDA 2002 patient survey found that only 5 percent of patients who visited their physician in the last three months did so due to a DTC advertisement.

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FDA issues guidance on how it will use pharmacogenomic data

FDA issued a new document—*Draft Guidance for Industry: Pharmacogenomic Data Submissions*—that when final will encourage drug and biologic developers to conduct pharmacogenomic tests during drug development and clarifies how FDA will evaluate the resulting data.

The guidance provides specific criteria and recommendations on submission of pharmacogenomic data to INDs, NDAs and BLAs. This includes information on what data are needed and how FDA will or will not use such data in regulatory decisions.

Because there is a need for scientific exchange between industry and FDA, the Agency is asking for voluntary submissions of research information. This data will help FDA gain experience as the field evolves. FDA advises sponsors to label voluntary submissions clearly. FDA will not use information from voluntary reports for regulatory decisions.

If a sponsor subsequently develops additional data that meet the criteria for submission for regulatory purposes, the Agency advises sponsors that such data should be submitted as explained in the guidance.

Pharmacogenomics deals with the small genetic differences that help explain why some people respond positively to a drug, while others don't respond, or may experience a side effect. Genetic differences also can predict variations in drug metabolism—how quickly or slowly a drug is eliminated from the body.

In the draft guidance, FDA says that the promise of pharmacogenomics lies in its potential to individualize therapy by predicting which individuals have a greater chance of benefit or risk—thus helping to maximize the effectiveness and safety of drugs. FDA believes that pharmacogenomic testing can be smoothly integrated into drug development processes.

This is FDA's first step toward integration of this new field into the process of demonstrating that new drugs are safe and effective. This guidance is intended to ensure that evolving regulatory policies and study designs are based on the best science; provide public confidence in this new field where scientifically appropriate; facilitate the use of such tests during drug development; and clarify for industry what types of pharmacogenomic data to submit to FDA.

"Using genomic testing to guide drug therapy will constitute a significant shift from the current practice of population-based treatment towards 'fine-tuning' individual therapy," said Center Director **Janet Woodcock, M.D.**

Currently, scientific understanding of phamacogenomics is most advanced in the drug metabolism area, and early results are expected in this field. However, FDA anticipates rapid evolution of additional uses. For example, pharmacogenomic testing may help identify cancers that have a high probability of responding to a particular medication or regimen. Pharmacogenomics may also be used to help track down the cause of certain rare, serious drug side effects.

FDA's Science Board at its April meeting endorsed Agency proposals to move forward with this guidance. The Agency also held public meetings and workshops in which the key issues for drug development were identified.

PIKE'S PUZZLER

Know your definitions

BY TONY CHITE

1. The Saffir Simpson Scale:

a. measures the category strength of a hurricane.
b. is a scale for weighing premature neonates.
c. is the most common grocery store produce scale.
d. converts human blood pressure in outer space to earth.

2. The word "icteric" is defined as:

a. a disease common to tropical fish.
b. a sudden seizure or stroke.
c. pertaining to or affected with jaundice.
d. a dermatitis with oozing pustules.

3. The word "hypopyon" is defined as:

a. spontaneous ignition of a flammable substance.
b. impairment of digestion.
c. abnormal decrease in production of saliva.
d. an accumulation of pus in the anterior chamber of the eye.

4. The word "irides" is defined as :

a. the plural of iris.
b. the ninth letter of the Greek alphabet.
c. the inflammation of a cuticle.
d. one of the smallest bones in the human body.

Key: 1 a ; 2 c; 3 d; 4 a

Tony Chite is a Pharmacist and CSO in the Division of Information Disclosure Policy.

DTC ad issues aired at public meeting

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One theme that arose repeatedly was the ineffectiveness of the brief summary in DTC print advertising in informing consumers about the indications, contraindications and risks of prescription medications.

According to the FDA survey, fewer than half of consumers who are interested in the drug read either all or almost all of the brief summary, while only 16 percent of consumers reported they typically read all or almost all of the brief summary.

Michael Roberts of Catalina Health Resource reported that more than 50 percent of research participants agreed that the brief summary is somewhat hard or very hard to read and understand. He presented a number of alternatives to the presentation of the brief summary, including the OTC Drug Facts labeling model adopted by FDA in 1999, a format also endorsed by Linda Golodner of the National Consumers League.

For complete information about the public meeting, including all presentation slides, please visit http://www.fda.gov/cder/ddmac/DTCmeeting2003.html.

Amie Braman and Kathryn Aikin are social scientists in DDMAC.

Compliance policy guide targets unapproved marketed drugs

(Continued from page 1)

law regarding so-called "grandfathered" drugs.

- Emphasize that illegally marketed unapproved new drugs must obtain FDA approval.
- Provide an incentive to be the first manufacturer to obtain approval for one of these drugs. After a grace period, FDA will consider taking enforcement action against unapproved competitors, which may result in *de facto* exclusivity.
- Avoid unnecessarily restricting patient access to useful medicines.
- Reiterate our risk-based criteria for enforcement action.

Our enforcement approach will give the highest priority to those products which pose the most risk to public health, either because they have inherent safety concerns or because there are alternative, FDA-approved treatments available. High-priority targets for enforcement will include:

- Products with potential safety risks.
- Products lacking any evidence of efficacy.
- Products that are clearly fraudulent.

Allowing continued marketing of unapproved drugs that compete against approved counterparts challenges the integrity of the drug approval system. Drugs that challenge the approval system will automatically fall into one of our high-priority enforcement categories. The continued marketing of these unapproved drugs also undermines the incentives needed to conduct the scientific studies to determine the safety and effectiveness of drugs.

Most of these drugs were first marketed before 1938, when FDA approval was not required, or between 1938 and 1962, when approval was based on safety alone:

- *Pre-1938 drugs.* Many pre-1938 drugs that are still marketed without FDA approval purport to be "grandfathered." Few of these, if any, would meet the legal test for continued marketing. FDA and the courts have taken a narrow interpretation of the grandfathering clauses, and the Agency has never formally recognized a drug as grandfathered. A drug would be disqualified from grandfathering if, after 1938, there were any changes to the product in formulation, dosage form, potency, route of administration, indication or intended patient population.
- *DESI drugs.* We initiated the Drug Efficacy Study Implementation to evaluate the effectiveness of drugs we had approved between 1938 and 1962 on safety grounds alone. These drugs—and those identical, related and similar to them—may continue to be marketed until our administrative proceedings evaluating their effectiveness have been concluded. After that point continued marketing is only permitted if an NDA is approved for each such drug. Under DESI, we reviewed 3,443 prescription drugs with 16,000 claims. We removed 1,099 from the market for lack of proven effectiveness. We currently permit continued marketing of a few DESI drugs whose proceedings are still pending.

At the request of Congress, we are examining whether any class or classes of prescription drugs might be regulated under a monograph system in lieu of requiring individual applications. Although we have considered and declined this approach on several past occasions, we will consider whether new, relevant factors affect our analysis as we re-visit the question.

Because the Office of Compliance doesn't have complete data on illegally marketed products and because the market is constantly changing, we will need the assistance of the Office of New Drugs and the Office of Pharmacoepidemiology and Statistical Science in helping to identify illegally marketed products for enforcement action.

David Horowitz is director of CDER's Office of Compliance

NCI, FDA to collaborate on speeding promising therapies to clinical trials

National Cancer Institute Director **Andrew C. von Eschenbach, M.D.,** and FDA Commissioner **Mark McClellan, M.D., Ph.D.,** announced on Nov. 12 two new collaborative initiatives to facilitate the development and use of better cancer treatments.

"We are working to get safe and effective cancer therapies to patients as quickly and inexpensively as possible," McClellan said. "Using modern information technologies to make our processes more efficient is a key approach to achieving this goal."

Specifically, the new initiatives will:

- Link cancer researchers around the nation electronically to FDA, reducing the time it takes for promising new drugs to enter clinical trials. Electronic submission of data should allow patients earlier access to experimental therapies as a result of shorter FDA processing time of IND applications.
- Initiate Cancer Fellowship Training Programs to develop a corps of physicians and scientists expert in clinical research, the regulatory approval process and translation of research breakthroughs to clinical practice.

These initiatives result from ongoing work from the Interagency Oncology Task Force established in May 2003 to improve the efficiency of all aspects of cancer drug development and regulatory review.

Investigators submitting INDs electronically to CDER will need to use the format for the electronic Common Technical Document (August 27, *Pike)*. The Center has posted technical specifications for the eCTD at http://www.fda.gov/cder/regulatory/ersr/ectd.htm.

"However, before submitting an official IND electronically to a review division, sponsors should send a sample eCTD to the Center," said **Gary Gensinger** from CDER's Office of Information Management.

"We will test the sample to ensure that in conforms to our eCTD specifications. The content of the sample won't be reviewed by an FDA reviewer."

Directions for submitting the sample eCTD were announced Sept. 1 and are at http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000027-vol1.pdf.