news along the pike

CENTER FOR DRUG EVALUATION AND RESEARCH

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VOLUME 8, ISSUE 5

INSIDE . . .

PIKE'S CORNERS . . .

20,000 pharmacies use Center's public education ads

Consumers to get messages when they pick up prescriptions

BY CINDI FITZPATRICK

About 150 million times in 2003, the nation's retail pharmacy customers will receive one of the Center's messages on using medicine wisely when they pick up their prescriptions. Beginning in August, Health Resource, a leading provider of newsletters, has been including our health promotion messages in three different newsletter products.

Two newsletters are distributed at the pharmacy and are customized to the patient and the prescribed medicine. One is for brand-name drugs, and the other is for generics. They are stapled to the bag containing the prescription. These newsletters appear in 20,000 pharmacies across the nation.

The third newsletter, a pilot program, is distributed in the health care provider's office.

The partnership with Health Resource gives us the capability to:

- Design messages appropriate for individual classes of drugs.
- Place messages in consumers' hands when they are most receptive to learning about medication use.
- Provide messages implicitly endorsed by consumers' most trusted health care professionals, their physicians and pharmacists.
- Obtain feedback on the number and kind of messages distributed.

The Division of Public Affairs in the Office of Training and Communications is coordinating the partnership. The messages can be keyed

(Continued on page 14)

CBER official highlights biologics review science

BY SHARON T. RISSO

Because the review of therapeutic drug and biologic products is being consolidated (October *Pike),* we in the Office of Therapeutic Review and Research in CBER welcome the opportunity to explain what biologics are, how they are regulated and who we are to our colleagues in CDER. While many details of the consolidation remain to be worked out, most of the people and products to be transferred to CDER will come from our office.

In this article, I will provide an overview of our current structure and regulatory science practices. While the preclinical and clinical development of drugs and biologics is similar, major differences exist in product structure, legislative authority, operational structure and review practices.

What are biologics?

Biologics are living organisms such as cells or bacteria, or large molecular structures derived from living sources such as human or animal cells and genetically engineered microorganisms. Many biologics are made using the biotechnology developed in the last quarter of

(Continued on page 11)

FDA seeks cooperative framework for microarray technology

Editor's note: For a basic description of microarrays, see page 12. For an update on the Human Genome Project, see page 2.

BY FRANK D. SISTARE, PH.D.

The potential medical applications of microarrays have generated much excitement—and some skepticism—within the biomedical community. Microarrays can identify thousands of genes or proteins rapidly and simultaneously.

Some scientists predict that within this decade microarrays will be routinely used in drug development and medical practice. They foresee microarrays aiding the selection, assessment and quality control of the best drugs for development. They also predict microarrays will be used in disease diagnosis and for monitoring the desired and adverse outcomes of treatment.

Making this vision a reality will be a challenge for the whole scientific community. Breakthroughs that show great promise at the bench often fail to meet the requirements of

(Continued on page 10)

JOE'S NOTEBOOK

HapMap: Beyond the genome map

I don't know if age is bringing me any wisdom, but it is surely bringing me the aches and pains from both sides of my family. We may be close to figuring out how this happens, according to the head of NIH's National Human Genome Research Institute. With the final map of the human genome due in April, **Francis Collins, M.D., Ph.D.,** outlined the next big genome project at the Center's Scientific Rounds on Sept. 30.

I once considered genetics the study of rare inherited diseases like muscular dystrophy. Now the term "genetics" is used more frequently to describe the study of single genes and their effects. The term "genomics" describes the study of the functions and interactions of all the genes in the genome.

Dr. Collins said that there are two universal principles of human genetics:

- Virtually all diseases have a genetic component.
- There are no perfect humans. All of us carry a significant number of DNA glitches.

Research shows that any two people are about 99.9 percent identical at the genetic level. It's the 0.1 percent difference that scientists expect will provide clues about common diseases as well as help predict drug responsiveness and drug adverse events.

Many of these differences are simple substitutions in the genetic code, like the spelling difference between "shirts" and "shorts." These substitutions of genetic letters are called single nucleotide polymorphisms or SNPs. (You're definitely in the know if you pronounce these as "snips.") The human genome is thought to contain at least 10 million SNPs, but most of them are medically insignificant, Dr. Collins said.

DNA is made up of four chemicals, called bases. Trying to map four variations at 10 million points is impractical. Fortunately, just as you can't find "sharts" or "shurts" in the dictionary, not all possible SNPs occur. Also, just as you find shirts and shorts in the same section of the dictionary or department store, SNPs are inherited in blocks rather than individually.

Because genetic variation among individuals is organized in "DNA neighborhoods" called haplotype blocks, Dr. Collins said his institute's latest big international collaborative project to map genetic variation is very practical. Scientists will only need to detect a few tag SNPs to identify a haplotype block. He predicts the HapMap project will be able to define all the common haplotypes in the human genome in two years. Then studies associating diseases or drug responses can be done with a "haplotype tag" set of about 250,000 SNPs.

The HapMap of a group of people known to respond to a drug could be compared to the HapMaps of those who don't respond or have adverse reactions to it. If enough of these associations can be made, scientists could zero in on specific genetic variations. Even without knowing specific genes, however, HapMap information could help select patients for clinical trials and tailor treatment to improve on drug efficacy rates and reduce adverse events.

You can borrow the video of the seminar from the Medical Library or read more about the international HapMap project at http://www.genome.gov/page.cfm?pageID=10005336.

Be sure to read the article by **Frank Sistare, Ph.D.,** (page 1) and look for more from the Office of Testing and Research in future issues.

Correction correction: Your editor is feeling especially dumb. Last issue's correction needs correcting. In my list of the faculty for carcinogenicity course volunteers in this column, I left out **Abigail D. Jacobs, Ph.D.** She was, of course, correctly listed in the article about the course by **Lawrence F. Sancilio, Ph.D.,** the very same issue! My apologies to Abigail for both omissions.

news along the pike

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

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OMBUDSMAN'S CORNER

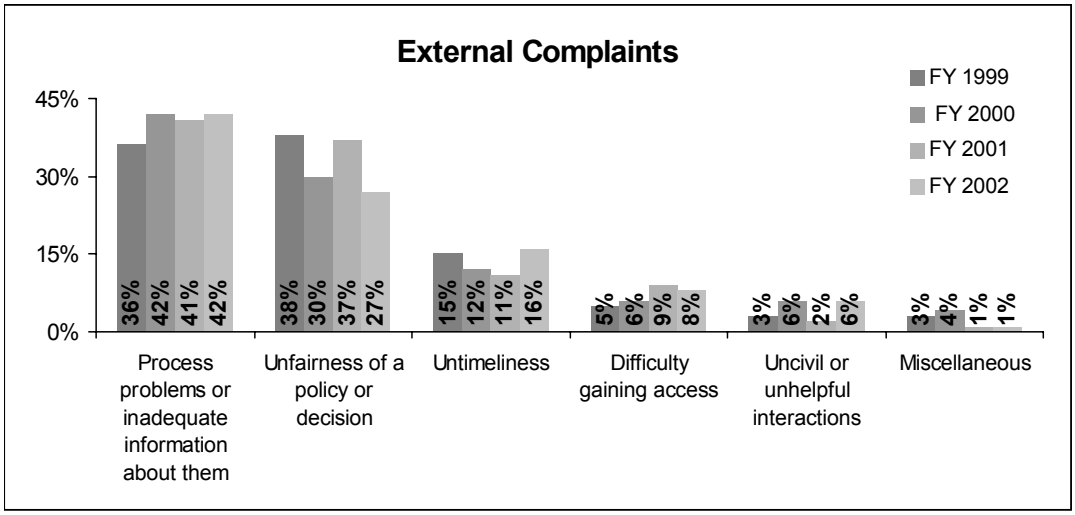
Annual report: Process issues remain on top of complaint list

BY JIM MORRISON

In my last annual report before leaving for pastures, greener or otherwise, I was hoping I could report that we had made significant progress in eliminating some of the more troublesome problems of the past.

Alas, that was not to be.

The number of cases and complaints rose moderately this past year, as did e-mail traffic. Of some concern was a significant rise in internal complaints, which, while still low, may reflect the cumulative effect of turnover in CDER's middle management, coupled with stress brought on by the increasingly tight timeframes of PDUFA II. Many reviewers and managers in CDER have felt pushed to their limits of capacity for workload and look forward to the added resources and realistic goals contained in PDUFA III.



As has been my custom, I tabulated external complaints according to six categories by percentage of total complaints. I compared the figures with three previous years to show trends better.

There are some trends worth noting. Unfairness became less of an issue, and timeliness bounced up, as did unhelpful interactions. I think these changes are further evidence of the workload stress that accompanied the last year of PDUFA II. I'm happy to report that complaints about uncivil interactions have dropped, and that the category was composed of the less offensive "unhelpful" variety of interactions.

Difficulty gaining access to CDER staff, in the form of meetings denied, phone calls not answered and late responses to correspondence (as well as delayed meeting minutes), has continued at an undesirable rate. At times this past year I have been snowed under, and I can sympathize with staff who just can't find the time to respond. But we really need to devote an extra effort to being more responsive. The people who try to contact us deserve better.

I plan to write one more column before I leave, but I would be remiss if I did not take this opportunity to thank the many people in CDER who have made my seven years as Ombudsman a truly rewarding experience. **Janet Woodcock** is at the top of my list, because she has strongly supported and appreciated the ombudsman function. The Center has made great strides under her leadership and will continue to do so in the future. I have received universal cooperation and help from CDER management and staff, for which I have been most grateful. Even the vast majority of those who have found themselves the subject of complaints have been forthcoming and cooperative, and, I hope, they have found it helpful that the role of the ombudsman is to listen to all sides of an issue and to get it resolved without recrimination or assigning blame.

All this thankfulness naturally leads to the question: "Why am I leaving?" Because it's time. In my 37 years with the FDA, I have never spent more than seven years in any one position. So it feels right for me to exit at this time. I don't know exactly what I'll be doing next year, but I have more goals and interests than I have time. Even after I depart, the people in CDER and their mission will always have a special place in my mind and heart.

We will be working to make the transition to a new ombudsman as smooth as possible, so stay tuned for more information.

Jim Morrison is the Center's ombudsman.

HHS to seek new legislation for mandatory pediatric drug testing

HHS announced on Dec. 16 that it will pursue rapid passage of legislation giving FDA authority to require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials on drugs and biologics. Clearer legislative authority is needed, instead of pursuing appeals in the courts.

The announcement came as the federal government decided not to appeal an October decision in the U.S. District Court for the District of Columbia, which held that FDA lacks the legal authority to impose certain requirements for pediatric testing on drug manufacturers. That decision has prevented the FDA from enforcing such requirements in the 1998 Pediatric Rule.

The Department outlined principles for the new legislation, saying it should include clear FDA authority for:

- Consultation between manufacturers and the FDA early in the drug development process regarding pediatric plans.
- Pediatric data to be provided by a manufacturer at the time of the new drug approval application or a timeline for pediatric data submission, if deferral is deemed appropriate.
- Pediatric studies of already marketed products.
- Creation of a new FDA Pediatric Advisory Committee.

INFORMATION TECHNOLOGY CORNER

Remote control via NetMeeting; e-CTD Viewer System on track

BY EBE UGWU

How would you like to have your wait time for a computer support technician greatly reduced? Well now you can. With the use of NetMeeting, OIT technical support staff can remotely diagnose, troubleshoot and fix some computer related issues at the click of a button when connected to your computer.

NetMeeting is a Microsoft remote control utility that OIT staff can use to connect securely to your computer and fix related issues, with you still retaining control over your computer. OIT Technical Support Staff will only remotely connect to your computer with your permission through a screen dialog. NetMeeting also offers you the ability to learn simple troubleshooting tips, as it can be used as a collaborative tool with audio and file sharing capabilities.

Recently, OIT completed tests on NetMeeting and is now ready to make it available to the CDER community. Please stay tuned for more information on how to take advantage of this new technology.

e-CTD Viewer System due this spring

BY: TIM MAHONEY

In OIT, we are working with developers and users from CDER, other centers and our partners in the International Conference on Harmonization to develop the Electronic Common Technical Document Viewer System. The system will allow FDA to validate and generate reports when e-CTDs are received in the Center and will provide reviewers a system to view, navigate, and download components of an e-CTD.

When guidance is released, this system will enhance and replace the current technologies used to review many of the Center's electronic marketing applications.

The e-CTD follows the structure and organization of the Common Technical Document (http://www.fda.gov/cder/guidance). OIT leads both the e-CTD development effort in ICH through the M-2 working group and internally though the Electronic Viewer System project.

A project change control board made up of reviewers from all disciplines in CDER and CBER has also been established to provide reviewer perspective and input on the decisions that affect the direction of the project. Project team members are OIT project managers and officers, M-2 working group experts from both CDER and CBER and contract staff.

OIT is working hard with our partners in ICH and the FDA to complete this first phase of e-CTD integration. Please look for more information such as guidance, training and promotional materials in the near future. Please contact me (MAHONEYT) for more information.

Tim Mahoney is the M-2 rapporteur and Electronic Viewer System project officer.

January OIT Training

Tuesday	Wednesday	Thursday
7	8 FormFlow (account Holders only) (C) 1-4 NEST (P) 9-12 NEDAT (P) 1-4	9
14	15 Excel (C) 9-12 DFS (C) 1-4	16 Outlook Email (C) 9-12 Outlook Calendar (C) 1-4
21	22 PowerPoint Intro (C) 9-12 PowerPoint Charts and Templates (C) 1-4	23
28 Word Intro (P) 9-12 Word Formatting (P) 1-4	29 Word Tables (P) 9-12	30

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

To protect patients, FDA adds 10 drugs with specific controls to Import Alert

FDA announced on Dec. 9 that it is restricting imports of certain prescription drugs that can be used safely only with specified controls in place. FDA's action involves adding the drugs to an existing Import Alert. The document alerts field personnel to the possible importation of these drugs, provides guidance as to their detention and refusal of admission into the United States and also advises U.S. Customs personnel to refer any attempted importation to the local FDA field office.

The drugs added to the alert are:

- Alosetron hydrochloride, indicated for the treatment of severe irritable bowel syndrome in women.
- Bosentan, indicated for the treatment of severe pulmonary arterial hypertension.
- Clozapine, indicated for the management of severe schizophrenia in patients who fail to respond to standard drug treatments for schizophrenia.
- Dofetilide, indicated for the maintenance of normal sinus rhythm in patients with certain cardiac arrhythmias
- Fentanyl citrate, indicated for the management of severe cancer pain in patients who are tolerant to opioid therapy.
- Isotretinoin, indicated for the treatment of severe recalcitrant nodular acne.
- Mifepristone or RU-486, indicated for the medical termination of early intrauterine pregnancy.
- Sodium oxybate, indicated for the treatment of cataplexy in patients with narcolepsy.
- Trovafloxacin mesylate or alatrofloxacin mesylate injection, an antibiotic administered in in-patient health care settings for the treatment of severe, life-threatening infections.
- Thalidomide, indicated for the acute treatment of the cutaneous manifestations of moderate to severe *erythema nodosum leprosum.*

The revised alert and a consumer advi-

(Continued on page 5)

Videoconferencing, teletraining let you be two places at once

By Pam Winbourne and Linda Emelio

At 8 a.m., you need to speak to European regulators at a meeting in Brussels; your division meeting is at 10:30 a.m. in Parklawn; and there's a presentation you must give downtown at noon. How can you do it all?

Videoconferencing has been the answer for many of you who are finding your schedules continually packed with competing needs.

The Office of Training and Communications provides the Center's videoconferencing and teletraining services with the Division of Public Affairs and Division of Training and Development sharing the duties.

Videoconferencing is a two-way, full-motion, full-color, electronic communication that permits two or more people in different locations to engage in face-to-face audio and video communication. Meetings, seminars and conferences are connected as if all of the participants were in the same room.

Videoconferencing

The Division of Public Affairs manages non-training videoconferences such as industry meetings and internal meetings. In addition, videoconferencing has enhanced our communications with the international health community. We have held videoconferences with people from all over the world, including those in Japan, Germany, Great Britain and Australia (for an example, see page 13).

Videoconferencing is also useful in emergency situations. When all travel was halted because of the September 11 terrorist attacks, we were still able to attend and speak at seminars by videoconference.

This is also a very useful tool at the end of the fiscal year or during continuing resolutions when travel money is unavailable or scarce. Even though we may not have funds to travel, we can still be accessible and available to industry and the health care community by videoconference.

To request videoconference services, contact:

- **Pam Winbourne,** (WINBOURNE, 7-3788).
- **Ayse Hisim,** (HISIMA, 7-7503).
- **Paul Neff,** (NEFFP, 7-1244).

Teletraining

When videoconferencing is used in an educational setting, we call it "teletraining." The instructor and students may be geographically separated and, therefore, need to rely on videoconferencing equipment for their interaction. The Division of Training and Development provides videoconferences of instructor-led classroom courses and satellite broadcasts to various CDER sites.

The Center began teletraining about five years ago by videoconferencing the CDER Seminars and Scientific Rounds to CDER buildings. You have the convenience of participating in these programs in your own buildings instead of traveling to the Parklawn Building each Wednesday afternoon.

Teletraining can be more cost-effective than classroom training, by reaching more people simultaneously. In CDER, we use it primarily for efficiency—to reduce travel time between buildings and allow more people to attend programs on specific topics.

Our goal in teletraining is to ensure that the educational setting remains interactive; that is, that the instructors can hear and see participants in other buildings, just as if they are in the same room.

At the same time, we use teletraining to expand the course offerings available to you. By connecting to satellite downlinks, we are able to offer courses from other federal agencies, such as the Centers for Disease Control and Prevention, the U.S. Army and the National Institutes of Health, as well as from technical and scientific associations offering courses on specific topics.

Here are examples of teletraining and satellite broadcast offerings within the last two years:

Internal teletraining

- International Seminar Series.
- Visiting Professor Lecture Series: Process analytical technology.
- Pharmacogenetics course.
- IMS Health: In Search of Solutions course.

Externally sponsored teletraining

- HHS and Parklawn chapter of Blacks in Government: Black History Month program.

Scientific broadcasts

- U.S. Army Medical Command: Biological and chemical warfare and terrorism/medical issues and response.
- Society for Nuclear Imaging and Drug Development: Positron emission tomography and its applications in drug development.
- FDA and the Drug Information Association: "CDER Live!"

Administrative broadcasts

- FDA/National Treasury Employees Union joint training: What managers and employees need to know about the collective bargaining agreement.
- OPM, the federal government's human resources agency: Federal long-term care insurance program.

The Division of Training and Development coordinates the Center's teletraining events. The division works with course organizers and instructors to plan and schedule the events appropriately.

The division also offers guidance to instructors in teletraining techniques such as camera awareness and interacting with participants at remote sites. The division also coordinates externally sponsored training events for CDER employees.

To learn more about teletraining or for information about administrative broadcasts, contact **Linda Emelio** (EMELIOL, 7-0997).

For information about scientific broadcasts, contact **Chris Nguyen** (NGUYENC, 7-1668).

Instructions on CDERnet

For information about setting up a videoconference or teletraining event and a list of the Center's sites equipped for videoconferencing, follow the Videoconferencing/Teletraining link at the top of the CDERnet homepage or go directly to http://cdernet/dcm/TELECONFERENCING.HTM.

Pam Winbourne is the Center's videoconferencing coordinator in DPA, and Linda Emelio is an education specialist in DTD.

Drugs added to Import Alert

(Continued from page 4)

sory are available at http://www.fda.gov/ora/fiars/ora_import_ia6641.html and http://www.fda.gov/oc/buyonline/consumeralert120902.html respectively.

Pharmaceutical science advisory panel notes 3 years of successes

BY MARY JANE MATHEWS

At the opening session of the two-day meeting of the Advisory Committee for Pharmaceutical Science held in October, **Helen Winkle,** Acting Director of the Office of Pharmaceutical Science praised the accomplishments of the current committee.

The committee advises the Center on relevant scientific issues. During the last three years, the committee made recommendations on the following:

- The food effects guidance.
- The Biopharmaceutics Classification System.
- Establishment of the Process Analytical Technologies Subcommittee. The advisory committee supported the new subcommittee as they met during the past year to work on issues with the potential to promote efficiency and reliability in drug manufacturing while reducing expenses.
- The draft guidance on dermatopharmcokinetics (absorption, distribution, metabolization and elimination of pharmaceuticals applied to the skin) and the change of focus to general bioequivalence methodology for these products. This work resulted in withdrawal of the draft guidance.
- The acceptability of the Product Quality Research Institute's project on blend uniformity, bringing the issue to a close. OPS will move ahead on the draft guidance document.
- Individual bioequivalence and replicate design which led to changes in the General Bioavailability/Bioequivalence Guidance.
- BA/BE and chemistry guidances for oral inhalation nasal products.

The committee participated in awareness sessions on other issues, including:

- Lactation.
- Polymorphism.
- Risk-based CMC review.
- Liposomes.

Winkle thanked, Vincent H.L. Lee, Ph.D., professor and chairman of the Department of Pharmaceutical Science at the University of Southern California, for his year of service as chair of the committee. She called Dr. Lee "a wonderful leader" who served the committee with dedication and much hard work.

"It was a great experience," Lee responded. "The diversity of the group was a key factor." It represents a strong partnership between regulators and scientists, he said.

During the two-day meeting, the committee listened to and discussed the issues surrounding several important scientific topics.

- Risk-based CMC review.
- Blend uniformity.
- Polymorphism.
- Aseptic processing.

The committee heard reports from the subcommittees under its leadership.

- The Non-Clinical Studies Subcommittee, which is being moved to the National Center for Toxicological Research, will be replaced by a new pharmacology/toxicology subcommittee (see below).
- The Process Analytical Technologies subcommittee, which met for its sunset session, laid the groundwork for a future manufacturing subcommittee.

Winkle announced that the new advisory committee chair will be Arthur H. Kibbe, Ph.D., chair and professor at the Department of Pharmaceutical Sciences, Wilkes University in Wilkes-Barre, Pa. Dr. Kibbe agreed to serve in this capacity for two years.

Mary Jane Mathews is a writer/editor in the Office of Pharmaceutical Science.

New advisory subcommittee to examine clinical pharmacology issues

The Advisory Committee for Pharmaceutical Science launched a new subcommittee to consider issues in clinical pharmacology.

The role of the Clinical Pharmacology Subcommittee is to advise and make recommendations on the "use of new data on emerging technology in clinical pharmacology as applied in the regulatory environment," according to **Lawrence Lesko, Ph.D.,** director of the Office of Clinical Pharmacology and Biopharmaceutics in the Office of Pharmaceutical Science.

At the panel's inaugural meeting in October, **Helen Winkle,** OPS acting director greeted the new members. "Dr. Lesko and I have had the dream of having this subcommittee for quite a long time now and it is really good to see it come to fruition," she said.

The acting chair is William Jusko, Ph.D., from the State University of New York at Buffalo School of Pharmacy.

Lesko said: "I recognize the talent that we have assembled." He acknowledged the willingness of both members and invited guests who agreed to participate in spite of their own responsibilities.

The topics for the first meeting covered three broad areas in which clinical pharmacology plays an important role in the agency: pharmacometrics, pharmacogenomics and pediatrics.

"We want to look at the way we analyze investigational pharmacokinetic studies to identify patient populations at risk," Dr. Lesko said the first topic on the agenda was the meeting's main item. he said.

Two aspects of risk were covered:

- *Risk assessment,* science-based estimates of a risk that is based on a population who may be over- or under-exposed to a drug.
- *Risk management,* the management of a potential safety or effectiveness issue by, for example, adjusting the dosing regimen to optimize clinical outcomes.

Peter Lee, Ph.D., OCPB, and **Jurgen Venitz, M.D., Ph.D.,** who is on sabbatical in OCPB from Virginia Commonwealth University, presented the topics for the morning session.

In the afternoon, the subcommittee heard presentations on pediatric dosing decisions from small pediatric trials using existing adult dosing information. **Rosemary Roberts, M.D.,** Office of Counter-Terrorism and Pediatric Drug Development, and **Arzu Selen, Ph.D.,** OCPB, presented the topics.

The group looked at the use of exposure-response relationships in a pediatric study decision tree that could provide ways to extrapolate adult clinical data for use in pediatric patients. Using this approach would avoid large-scale clinical

(Continued on page 7)

LETTER FROM AFGHANISTAN

CDER medical officer coordinates HHS humanitarian efforts

BY DAVID GAN, M.D., DR.PH, MPH

KABUL, Afghanistan—Things here are very tough. In November, several rockets were fired on our compound and seven on the German compound. Those Taliban and al Qaeda always want to kill us. Fortunately, the precision of their rockets is very poor, and nobody was injured.

Overall, 99 percent of the Afghanis like us. Wherever we go, people say "thank you" with their thumbs up. The commander here appointed me as medical director for the multinational Coalition Joint Civil Military Operations Task Force.

The task force provides niche humanitarian projects throughout the country that are not being accomplished by the greater humanitarian community. We are careful to coordinate its efforts with the Afghan agencies and other humanitarian and relief agencies.

A majority of our projects are accomplished with Afghan labor and Afghan materials to maximize the benefit to the local economy.

My job is very challenging, and I enjoy what I am doing. I work very closely with the Afghan Ministry of Health, the U.S. Department of Health and Human Services, the U.S. Department of Defense, the World Health Organization and private organizations to rebuild the Afghan health care system.

Projects we are working on include rebuilding:

- Hospitals.
- A pharmaceutical plant.
- The national disease surveillance system.
- The disease outbreak investigation infrastructure.

Our commander appointed me as the coordinator for all HHS's possible projects, and I am working hard to assist HHS to be success here.

HHS and DoD sent a 10-member delegation to Kabul in early December to develop projects. I developed their itinerary and coordinated all their activities.

HHS Secretary **Tommy G. Thompson** signed an agreement with the Afghanistan Ministry of Public Health to help redevelop the country's medical infrastructure and continue to improve essential health care services and the social service delivery system.

Thompson is also working with DoD to develop some joint projects. The Army is rebuilding some hospitals here, and HHS is responsible for training and equipping the hospitals.

HHS wants to establish a formal relationship with the Afghan Ministry of Health to focus on:

- Improving maternal, infant and child health.
- Securing and restoring hospital infrastructure.
- Providing safe water and sanitation systems.
- Building epidemiological services.
- Developing mental health services.

As a soldier serving in Afghanistan, I am reminded of how much we appreciate the little things that are so easily overlooked in our society. Things like water—hot water, showering, modern bathrooms, clean water from a faucet—clean air, workable phone system, nice roads, air conditioning, cars and food. We should thank God for what we have in America.

Traffic in Afghanistan is complicated and dangerous. Yes, they have cars, trucks and motorcycles in their cities, but they also have hand-powered carts, donkeys, horses and on the outskirts of town camels and sheep.

The weather here is OK. It's very cold at night. It's warm during the day. I run every morning from 6 a.m. to 7 a.m. We do not have any days off, not even weekends. I put in 16 hours a day. I stay busy, keep a positive attitude and make my time pass quickly.

It's so difficult to work here. The phone system doesn't always work. I cannot go out by myself. I have to wear my body armor and carry my weapon all the time. It's a new experience and an adventure. I am well respected here, and I am trying hard to fulfill my duty as a soldier and as a citizen. It's our belief that helping the Afghan people is helping American interests.

My family is doing very well with the support from FDA, our church and our community. My son, Kevin (Gan Wei), is doing very well. He made the top six in the national Siemens Westinghouse Science, Math and Physics competition and will compete for first place.

He was co-author on a paper published in *Science* Express Internet version in October and *Science* paper version in November. He had a perfect 1,600 score on his SAT test. However, he missed the deadline to submit his paper for the Intel competition by five minutes. I am a little disappointed. If I were home, this would not have happened. Anyway, I am very satisfied with his success.

I truly miss my work at FDA, and I am looking forward to coming back in August. The Division of Scientific Investigations has done a lot to support me and my family for my deployment to Afghanistan. Thank you very much for your support. It means a lot to me.

David Gan, an Army Reserve major, is currently medical director of the Coalition Joint Civil Military Operations Task Force in Afghanistan. When he is in Rockville, he is a medical officer in the Division of Scientific Investigations in the Office of Medical Policy.

New advisory subgroup

(Continued from page 6)

trials in children and expedite access to drugs for children.

The use of genetic tests to determine drug dosage and administration was the last topic of the day. The model compound used for discussion was mercaptopurine, an oral drug used to maintain remission in children with acute lymphocytic leukemia. Before the advent of genetic testing, the drug caused serious and sometimes fatal adverse events for the one in 300 patients unable to metabolize mercaptopurine because of a genetic defect. Richard Weinshilboum, M.D., Mayo Clinic, Rochester, Minn., and Mary Relling, Pharm.D., St. Jude Children's Research Hospital, Memphis, Tenn., presented the information.

For the next meeting Dr. Lesko hopes to present updated information on these topics and add other relevant topics for the subcommittee's consideration.

CDER group targets drug safety awareness in nursing community

BY E. JANE MCCARTHY, CRNA, PH.D., FAAN

A group of the Center's nurses is developing the Nurses Network to further CDER's mission of improving patient safety with regard to drug products.

The goal of our new program, coordinated by the Office of Training and Communications, is to have Center nurses educate nurses in the community about drugs, patient safety and the role of FDA and the Center.

Our objective for 2003 is to inform nursing organizations about the drug approval process and how nurses can help improve risk management by reporting adverse drug events through MedWatch.

Specifically, we will educate community-level nurses about FDA's role in patient safety by identifying nurses' organizations interested in receiving FDA brochures, Web site linkage, lectures and posters. Through these activities, nurses outside of FDA will learn about what nurses do in CDER. Also, we will gain information about the impact of FDA policy decisions on clinical nursing practice.

E. Jane McCarthy, CRNA, Ph.D., FAAN, and **Debra Rose, R.N., M.A.,** from OTCOM are the chairpersons of this program.

Other members of the group are:

- **Daryl Allis, FNP, M.S.,** Office of New Drugs, Division of Cardio-Renal Drug Products.
- **Robin Anderson, R.N., MBA,** OND, Division of Special Pathogen and Immunologic Drug Products.
- **Christine Bechtel, R.N., MSN,** Office of Executive Programs.
- **Sandra Birdsong, R.N., BSN,** Office of Drug Safety, Division of Drug Risk Evaluation.
- **Jane Dean, R.N., MSN, CCRC,** OND, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products.
- **Julieann DuBeau, R.N., MSN,** OND, Division of GastroIntestinal and Coagulation Drug Products.
- **Cynthia Fitzpatrick, R.N., BSN,** Office of Training and Communications, Division of Public Affairs.
- **Joan Flaherty, R.N., M.S.,** Office of Counter-Terrorism and Pediatric Drug Development, Division of Counter-Terrorism.
- **Tia Frazier, R.N., M.S.,** OND, Division of Over-the-Counter Drug Products.
- **Nancy Halonen, R.N., BSN, CDE,** OND, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products.
- **Rita Hassall, R.N., MSN,** Office of Pharmaceutical Science.
- **Deborah Henderson, R.N., MSN,** Office of Executive Programs.
- **Rubynell Jordan, R.N., MPA,** Office of Executive Programs.
- **Alice Kacuba, R.N., MSN, RAC,** OND, Division of GastroIntestinal and Coagulation Drug Products.
- **Lorene Kimzey, R.N., BSN,** OND, Office of Drug Evaluation IV.
- **Carol Krueger, R.N., BSN,** Office of Compliance, Division of Prescription Drug Compliance.
- **Christine Lincoln R.N., M.S., MBA,** OND, Division of Anti-Viral Drug Products.
- **Janet Norden, R.N., MSN,** Office of Medical Policy.
- **Nina Nwaba, Pharm.D.,** Office of Generic Drugs, Division of Bioequivalence.
- **Martha O'Lone R.N., BSN,** Center for Devices and Radiological Health.
- **Jeff O'Neill, R.N., ACRN,** OND, Division of Anti-Viral Drug Products.
- **George C. Rochester R.N., Ph.D.,** Office of Biostatistics, Division of Biometrics III.
- **Terri Rumble, R.N., BSN,** OND, Office of Drug Evaluation V.
- **Laura Shay, CANP, M.S.,** OND, Division of Over-the-Counter Drug Products.
- **Leslie Stephens, R.N., MSN,** ODS, Division of Surveillance, Research and Communications Support.
- **Sakineh Walther, R.N., BSN,** Office of Compliance, Division of Prescription Drug Compliance.
- **Leslie Wheelock, R.N., MSN,** OTCOM, Division of Training and Development.
- **Su Yang, R.N., MSN,** OND, Division of Metabolic and Endocrine Drug Products.

If you are a CDER nurse and this new program interests you, send an e-mail to **Ayanna Hill** (HILLA), in the Division of Training and Development, and she will add you to the distribution list of interested nurses. For all other information, call Jane McCarthy (7-3492).

E. Jane McCarthy works in OTCOM's Division of Training and Development.

FDA Web site for Bioterrorism Act provides updates, e-mail list

BY JOHN HENKLE

FDA has added a new page to its existing bioterrorism Web site to provide information on the Agency's efforts related to the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, known as the Bioterrorism Act.

The act also included the reauthorization of prescription drug user fees.

The new page on the Bioterrorism Act provides easy access to the Act, the provisions of the law related to FDA and the Agency's activities to implement these provisions.

Among the Web site's features are:

- Access to FDA updates on its activities related to the Bioterrorism Act through a free subscription to a directed e-mail list.
- An overview of the Bioterrorism Act, including those aspects that most involve FDA such as protecting the nation's food, drug and biologic supplies.
- FDA's plans for implementing the Act.
- Summaries of the provisions related to FDA as well as links to related guidance documents, Federal Register notices and dockets.

The new FDA Bioterrorism Act site is at http://www.fda.gov/oc/bioterrorism/bioact.html.

FDA's main bioterrorism site is http://www.fda.gov/oc/opacom/hottopics/bioterrorism.html.

John Henkle is a public affairs specialist in FDA's Office of Public Affairs.

Pharmacologists work with NIH group on reproductive toxicology

BY JOHN LEIGHTON, PH.D.

For many decades, we have known that drugs and chemicals have the potential to affect human reproductive abilities and the developing fetus. The effects of thalidomide and DES (diethylstilbesterol), for example, are well-known. Animal testing can identify human reproductive risks for these and many other compounds.

In CDER, our pharmacologists and toxicologists are now actively working to identify chemicals under our authority that may not have been fully evaluated with animal testing. We will nominate them to the Center for Evaluation of Risks to Human Reproduction for further study.

A part of the NIH, CERHR provides uniform, scientifically based assessments of the potential of adverse events on reproduction and development to humans that may result from exposure to chemical agents. They do this through rigorous evaluations of the scientific literature by independent panels of scientists.

CERHR, a 4-year-old initiative of the National Toxicology Program, was developed because of concerns from the public, health professionals and environmental scientists that exposure to chemicals may create unknown risks for human reproductive health.

The National Toxicology Program is a part of the NIH's National Institute of Environmental Health Sciences.

Several chemicals nominated by outside groups for study this past year were products regulated by CDER. On an *ad hoc* basis, our pharmacologists in the responsible review divisions have been providing background information to evaluate reproductive toxicity studies that have been completed for the nominated products.

The coordinators for FDA's efforts on this initiative are **Steven Galson, M.D.,** CDER's deputy director, and **Bernard Schwetz, DVM, Ph.D.,** FDA's senior advisor for science. They have provided our information to the CERHR.

Our pharmacologists realized that a more rational process was needed and thus formed a reproductive risk-working group with the goal of identifying chemicals for future evaluation. This effort is led by **Robert Osterberg, Ph.D.,** acting associate director for pharmacology and toxicology in the Office of New Drugs, and **Frank Sistare, Ph.D.,** acting director of the Office of Testing and Research in the Office of Pharmaceutical Science.

Abby Jacobs, Ph.D., a supervisory pharmacologist in the Division of Dermatologic and Dental Drug Products, searched various databases to update previous searches that identified drugs labeled Pregnancy Category C. These initial searches were performed by **Ita Yuen, Ph.D.,** and **James Farrelly, Ph.D.,** both pharmacologists in the Division of Anti-Viral Drug Products.

Pregnancy Category C includes not only drugs that have been tested and the animal findings deemed positive but also drugs that may never have been tested. Dr. Jacobs, therefore, refined the initial search to identify those Category C drugs that have inadequate or no animal data and that lack human data to support more informative pregnancy labeling.

Similarly, Dr. Osterberg identified over-the-counter drugs that lack sufficient information on reproductive toxicity.

A multidisciplinary staff is being formed to further investigate the relative levels of concern among products identified by Drs. Jacobs and Osterberg. This analysis will require the professional judgment of division pharmacologists who work with these product classes.

The Informatic Computation Safety Analysis Staff in the Office of Pharmaceutical Science, directed by **Joseph Contrera, Ph.D.,** will also analyze and prioritize the teratogenic potential of candidate compounds using their structure activity relationship software (April 1998 *Pike* and February 2000 *Pike).*

With this more formal and rational approach, we anticipate being able to identify data gaps and prioritize the nomination of chemicals for CERHR's study and partner with CERHR in protecting the public health.

Others from CDER involved in this initiative not already mentioned are **Joseph Hanig, Ph.D.,** a supervisory pharmacologist in the Division of Applied Pharmacology Research, **Asoke Mukherjee, Ph.D.,** a pharmacologist in the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, **Nakissa Sadrieh, Ph.D.,** associate director for research policy and implementation in OPS, **Karol Thompson, Ph.D.,** a lead pharmacologist in the Division of Applied Pharmacology research, and myself.

John Leighton is supervisory pharmacologist in the Division of Oncology Drug Products.

Pike's Puzzler: Know your medical terminology

BY TONY CHITE, P.D.

1. *Cutis anserina* is also known as:

a. hangnail
b. goose flesh
c. sunburn
d. lockjaw

2. *Singultus* is also known as:

a. laryngitis
b. an amputated finger
c. hammertoe
d. hiccups

3. *Epistaxis* is also known as:

a. indigestion
b. suppression of a secretion
c. embryonic formation of bone
d. nosebleed

4. *Epistasis* is also known as:

a. suppression of a secretion
b. nosebleed
c. desquamation of the epithelium
d. surgical incision into the perineum and vagina to prevent traumatic tearing during delivery.

5. *Syncope* is also known as:

a. manic depression
b. drowning
c. fainting
d. inability to cope

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

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

FDA seeks cooperative framework for microarray technology

(Continued from page 1)

clinicians and regulatory scientists.

The development of a cooperative framework among regulators, product sponsors and technology experts will be essential for realizing the revolutionary promise that microarrays hold for drug development, regulatory science, medical practice and public health.

Microarrays have become central to progress in genetic research. They are now being applied to protein research. Regardless of the application, microarrays can provide thousands of individual measurements and paint an intricate and complex snapshot of biological properties of the cell, tissue or organ.

Drug development and medical practice are likely to be improved by identifying the genes and proteins that can be linked to disease states, differential responses to drugs and alterations in normal drug metabolism.

Risk-benefit evaluation

At FDA, we anticipate the expansion of microarray-based technologies. In evaluating the applications using this technology, our guiding principle will be an individual analysis of the benefits and risks or each new product.

On the one hand, we want to facilitate technologies like microarrays that provide volumes of information. On the other hand, we don't want to introduce misleading information into a time-tested system that assures consumers that FDA-approved drugs, biologics and devices will improve their health.

Reasonable concerns exist about the use of data derived from microarray technologies for medical applications. Although data are improving, there is currently no convincing evidence to support a high level of intralaboratory reproducibility, reliability, precision and accuracy of data derived from DNA microarrays.

Furthermore, while our understanding of gene function and gene product interactions is evolving rapidly, our ability to measure end points has outpaced our ability to explain all of them convincingly. FDA and industry will need to collaborate closely to make sure that drug development isn't bogged down seeking answers to a large number of complex endpoints that are neither easily explained nor reliably reproduced.

NIH's National Human Genome Research Institute (page 2) promises to identify DNA markers for all the common variations in the human genome within two to three years. Researchers may then be able to make statistical linkages of these DNA markers to diseases or drug responses. A persuasive linkage requires a well-understood, genome-based pathophysiological mechanism to predict differences. However, it is likely that associations will be observed without a clear pathophysiological mechanism. This type of linkage is less desirable but may be convincing with a more substantial dataset.

Whether these associations become surrogate markers for disease or drug response will depend on several factors, including the degree to which changes in DNA markers can predict changes in clinical outcome.

Individual measurements from a single microarray platform do not share the same precision, sensitivity or specificity. For example, even for a microarray with 99 percent accuracy, readouts of 10,000 data points would yield 100 false positive signals based solely on random chance. Scientific consensus and standards are needed to develop, evaluate and accept new statistical models for establishing the significance of linking gene and protein pattern analyses to more conventional diagnostic end points or outcomes.

Agency, industry collaboration

Microarray technologies are in a constant state of evolution, and new developments appear at a regular pace. A continually evolving technology presents difficulties for standardization and consensus development.

A cooperative two-day workshop was held in May 2002 and considered processes by which the FDA and industry could work together to develop mechanisms for systematically sharing and learning from exploratory microarray data from products under development.

The workbook from the workshop, Pharmacogenetics and Pharmacogenomics in Drug Development and Regulatory Decision-Making, is available at http://www.fda.gov/cder/calendar/meeting/phrma52002/workbook.pdf. The workshop was co-sponsored by FDA, the Pharmacogenomics Working Group, comprising major companies engaged in pharmacogenomics research, and the DruSafe Group of the Pharmaceutical Research and Manufacturers of America.

In addition, through efforts coordinated under the International Life Sciences Institute (http://www.ilsi.org/file/genomics.pdf) and the Human Proteome Organization (http://www.hupo.org), FDA, industry and academic researchers have been cooperating to develop strategies and processes for microarray applications and, in some cases, have been generating, sharing, analyzing and debating interpretations of collaborative experimental data across different platforms.

To ensure that FDA does not hinder clinical transfer of this important technology, we are committed to evaluating new diagnostic applications using least-burdensome thresholds, as outlined in the FDA Modernization Act of 1997.

As a result of the May workshop, the directors of FDA's medical product centers and the directors of Agency groups involved in microarray scientific research collaborated on an in-depth article describing the regulatory science perspective on microarrays. It was published in a December supplement to *Nature Genetics.* The full article in HTML is available online at http://www.nature.com/cgi-taf/DynaPage.taf?file=/ng/journal/v32/n4s/full/ng1029.html. A PDF version is at http://www.nature.com/cgi-taf/DynaPage.taf?file=/ng/journal/v32/n4s/full/ng1029.html&filetype=PDF.

In future issues of *News Along the Pike,* we will examine in more depth the cutting edge research on microarrays taking place in CDER's laboratories in the Office of Testing and Research in the Office of Pharmaceutical Science.

We look forward to participating in the evolution of medical applications from the new fields of science ushered in by DNA and protein microarrays.

Frank D. Sistare is currently acting director of the Office of Testing and Research and director of OTR's Division of Applied Pharmacology Research.

Biologic review focuses on production, drug substance

(Continued from page 1)

the 20th century and often represent the cutting-edge of biomedical research. They may offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available, such as rheumatoid arthritis and multiple sclerosis.

Some biologics you may be familiar with are recombinant alteplase (Activase), abciximab (ReoPro), epoetin alfa (Epogen), trastuzumab (Herceptin), (rituximab) Rituxan, ibritumomab tiuxetan (Zevalin), etanercept (Enbrel), and a variety of interferons such as interferon alfa-2b (Intron), peginterferon alfa-2a (Pegasys) and interferon beta-1a (Rebif).

Most biologics are complex mixtures of large proteins that are not easily identified or characterized. The active drug substance may be produced along with other isoforms and intermediate proteins. These production by-products are frequently biologically active and impact both safety and efficacy. Biologics are heat sensitive and are unable to withstand the robust purification steps typical of synthetic drug manufacturing. Often the final drug product cannot be directly tested for purity or potency. Because of this, much of our review must focus on production and characterization of drug substance.

Legislative authority

Federal regulation of biologics in the United States began in 1902 and predates regulation of human drugs by four years. Although drug and biologic regulation have different basic statutes, the development of regulatory practices for both types of products has followed a similar, parallel path. Biologic products are predominantly regulated by the Public Health Service Act of 1944, but they are also subject to provisions of the 1948 Food, Drug and Cosmetic Act.

The PHS Act emphasizes the importance of manufacturing control for products that cannot be defined. For human drugs, it is the final drug product that is regulated. We regulate biologics from the time they are "propagated," which places a stronger emphasis on drug substance. The purity, consistency, safety, efficacy and stability of biologics are dependent on clearly defining and adhering to the processes described in an application.

The PHS Act provides important flexibility in regulating biologic products. It gives us authority to suspend licenses immediately when there is a danger to the public health. Because the FD&C Act defines biologics as drugs, we use that law for certain administrative procedures and labeling requirements. That law also gives us injunction and seizure authorities.

Once manufactured, biologics may be subject to lot release, that is they are tested and reviewed by FDA before being released to the market. We typically grant waivers to the lot release requirement for therapeutic biologics that are made by recombinant DNA technology or are monoclonal antibodies. However, if a product is poorly characterized or has poor production controls, we can place it on lot release and work with the company to correct problems.

Who we are

OTRR has four divisions: two are product oriented and handle product issues; one handles issues related to pharmacology and clinical trial design and analysis; and one provides project management for application review, quality control and policy. We use a product-oriented organization rather than the disease entity organization found in CDER.

The Division of Monoclonal Antibodies and the Division of Therapeutic Proteins are laboratory-based groups where our scientists review applications for product characterization and production issues. They also perform hands-on research. The staff consists of both researcher/reviewers and full-time reviewers.

Our research relates to issues impacting the safety, purity, potency and effectiveness of biological products. Because our reviewers are also performing cutting-edge research with the technology used to produce biologics, they are able to help sponsors grapple with complex production issues.

The Division of Clinical Trial Design and Analysis is our largest division and home to our pharmacologists, toxicologists and medical officers. Because a biologic frequently has indications across a spectrum of diseases, we find it efficient to keep our clinical experts together to readily exchange information. Our clinical expertise is varied and includes specialties in oncology, cardiology, neurology, internal medicine, radiology, rheumatology, infectious disease, and pulmonology.

The Division of Application Review and Policy has our project managers and is our quality control unit. Keeping our project managers together helps ensure consistency in information we relay to sponsors and applicants. They also maintain and edit our databases and work on policy issues for the office and the center.

Our review teams also have members from other offices within CBER including, statisticians, facility and equipment experts.

Biologic drug development

We have been historically "user friendly," open and transparent to the biotechnology industry. Most biotechnology companies are small and were basically built on a scientific research model. Drug development is new to many of these firms and getting a product to market may be a big hurdle for them. We meet frequently with industry and especially like to meet prior to the filing of an investigational new drug application.

Because many biologics are human-specific proteins, testing them in small animal models such as rats may not be meaningful. We try to use preclinical testing that provides insight on how the protein works in humans.

We also encourage manufacturers to develop a potency assay at the pre-IND phase as a foundation for dosing studies. In most cases, a simple measuring for quantity may be inadequate as a potency measure. Without good animal or other preclinical models, the first introduction of a biologic into humans is a big step. Biologics are placed on clinical hold much more frequently than drugs. For example, in fiscal year 2001 we had 125 INDs on clinical hold compared to 34 for CDER.

Establishing efficacy in clinical trials for biologics is very similar to that for drugs. In Phase II, we emphasize adequate dose ranging studies and identification of

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FDA research vital to safety of biologic products

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sound clinical endpoints.

Our goal for Phase III is to have identification of the appropriate patient population and sound trial design. We also push to have the biologic completely characterized and in its final manufacturing stage. Scaling up from laboratory production to full-scale manufacturing is not as predictable as it is for drugs. Although many biologics are natural human proteins, they may have serious side effects such as immunogenicity or suppression of the body's natural defense mechanisms. Even minor changes in manufacturing can affect a biologic's immunogenicity.

Manufacturing oversight

We focus on biologic safety in several ways. Many biologics are potent drugs, and we watch them carefully once they are marketed. Once again, we feel our structure offers an advantage. Because many have multiple indications, our medical officers from different specialties are able to rapidly pick up adverse event signals from ongoing clinical studies as well as from postmarketing surveillance. We work directly with applicants to modify labeling as needed.

Our research has also been vital to the safety of biologics. We research how products interact in the body and how cells communicate. We are working everyday with products similar to those the industry is studying and manufacturing and are able to provide insights to the industry. Our reviewers may be less conservative in allowing studies to go forward because they know where the risks are and can help applicants develop programs to monitor high-risk situations. There have been no market withdrawals of biotech products for intrinsic safety reasons.

Our staff are also deeply involved in field inspections. Our product reviewers participate in all preapproval inspections and many serve as product expert members of Team Biologics in conducting post-approval inspections. Team Biologics has a small cadre of 12 Office of Regulatory Affairs field inspectors with experience and expertise in biologics. They are located in the different districts but report to headquarters for Team Biologics activities and assignments.

Having a dedicated team that utilizes our product expertise helps us make the best use of limited resources. While on inspection, our product reviewers can focus on issues that are key to ensuring purity and potency. They can also assist the field investigator in evaluating the significance of any irregularities.

We look forward to working with our CDER colleagues on these and other issues in the months and years to come. We hope to share more information about us and our products in future issues of *News Along the Pike.*

Sharon Risso is deputy director of the Office of Therapeutic Review and Research in CBER.

Microarrays—Enabling technology for advances in gene, protein science

BY NORMAN "JOE" OLIVER

Biomedical knowledge advances in tandem with analytical technologies. Using traditional methods, scientists are able to look at expression of a relatively small number of genes or proteins at a time. Microarrays are the enabling technology of the vast expansion of knowledge in genomics and proteomics. The regulatory science implications of this technology are discussed in the article by **Frank Sistare, Ph.D.** (page 1).

The basic principle behind microarrays is miniaturizing current testing systems. This allows scientists to perform thousands of test reactions on a small surface using a small amount of materials, including samples from patients.

DNA microarray technology, for example, exploits the ability of messenger RNA to bind to the DNA sequence that mirrors the gene from which it originated.

With few exceptions, every cell in your body contains a full set of your chromosomes and identical genes. In any one of your cells, however, only a fraction of your genes are "expressed" or turned on. That expressed subset makes each cell type unique, such as a liver or heart cell. The messenger RNA molecules expressed in a cell are the building blocks of the proteins that perform most of the cell's critical functions.

DNA microarrays are small, solid supports, such as glass microscope slides, with thousands of genes or bits of DNA attached at fixed locations. A molecule of messenger RNA and its matching DNA fixed to the slide will "hybridize" or lock together. Scientists can use microarrays to study the kinds and amounts of messenger RNA produced by a cell, which in turn provides insights into how the cell responds to its changing needs.

Gene expression allows a cell to respond dynamically to external stimuli and its own changing needs. This acts as an "on and off" switch to control which genes are expressed and as a "volume control" to increase or decrease the level of expression of particular genes.

A microarray reader or scanner can be used to identify how thousands of individual genes are expressed differently between normal and diseased cells or between control and treated animal tissue. Messenger RNA molecules from diseased cells are labeled with red fluorescence, and molecules from normal cells are labeled with green fluorescence. They are then co-hybridized to the same DNA microarray. Spots on the slide with DNA expressed in common by both diseased and normal tissues will fluoresce with both colors and be detected equally. RNA present only in the diseased cells will fluoresce red, and RNA present only in the normal cells will fluoresce green. Spots with DNA unexpressed in both types of tissue are dark.

The fluorescence is read by a laser scanner. The fluorescence intensity, reflecting the expression level from both channels, is recorded separately. The relevant individual gene expression level is presented as the ratio of red intensity to green. Using this method, large studies have been performed to characterize the gene expression profile of various tissues in the context of a variety of physiological and pathological states.

The technology is not limited to genes and their expressed messenger RNA

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Top McClellan priorities: homeland security, safety, information

(Continued from page 14)

adverse events. There are two parts to doing this: One part is getting better information; another part is improving information and education efforts."

The new commissioner concluded the interview at CDRH by saying: "One of the things that I've come to know in the few weeks that I've been here is that not only do we have a very difficult and very complex mission that we always need to be challenging ourselves on how to address most effectively but we have some really talented people working on it. These are people who are not only highly skilled in what they do, but very dedicated to what they do and that's what gives me the most confidence in going forward in meeting the tremendous challenges ahead for FDA. And also the most pleasure frankly in having the opportunity to be Commissioner of an agency where there are so many highly skilled people who are so dedicated to the mission of promoting and protecting the public health."

The Commissioner's Office and FDA's Office of Management have set up an e-mail address, fda.ideas@fda.gov, where employees can submit ideas they feel will improve the Agency.

Sherunda Lister is a public affairs specialist in the Office of Training and Communications.

McClellan stresses need for new facilities at White Oak ceremony

BY NANCY SMITH, PH.D.

A ceremony on Nov. 15 at the Federal Research Center in White Oak celebrated the groundbreaking for the CDER Office Building, scheduled for completion in 2005.

Speakers included new FDA Commissioner **Mark McClellan, M.D., Ph.D.,** Deputy Commissioner **Lester Crawford, DVM, Ph.D.,** Stephen Perry, administrator of the General Services Administration, Montgomery County Executive Doug Duncan and Rep. Steny Hoyer of Maryland's Fifth District. The Shades of Blue Jazz Combo from Springbrook High School provided music.

Dr. McClellan, in his first address since being sworn in on Nov. 14, stressed the need for excellent facilities to allow FDA staff to carry out their mission of protecting the public health.

"Our mission depends on a solid cadre of experienced scientists, physicians, mathematicians and other highly qualified and dedicated professionals," Dr. McClellan said in prepared remarks. "Their expertise is essential for making our regulatory decisions balanced and fair, and for keeping us on the cutting edge of the technology and sciences used by industry.

"As FDA Commissioner, it is one of my foremost goals to make sure that the FDA's working environment encourages creativity, efficiency and superior performance—an environment in which the FDA functions effectively as a single agency that consistently supports top-quality work by all of its employees. One important element of recruiting and retaining the best FDA workforce is a first-class, modern workplace."

The CDER Office Building will be the second of 14 planned interconnected buildings on a campus-like setting that will eventually be home for most of FDA. The buildings will be located on 130 acres at 10903 New Hampshire Ave. in Silver Spring. Phase One of the project, the CDER Laboratory, is currently under construction and is scheduled to be ready for occupancy in October.

Photographs taken at the ceremony are at: http://www.fda.gov/pike/NovDec2002.htm#photo.

Nancy Smith is director of the Office of Training and Communications.

FDA participates via satellite in European workshop on small trials

BY JOHN FRIEL

On Oct. 22, FDA participated in a trans-Atlantic workshop sponsored by the European Agency for the Evaluation of Medicinal Products on clinical trials conducted in small populations. The formal title of the conference was "Workshop on Methodological Aspects of Clinical Trials for Efficacy Evaluation in Small Populations".

Dr. Marlene Haffner, director of FDA's Office of Orphan Products Development, participated in person while others from throughout the Agency did so through CDER videoconferencing facilities in Parklawn, Woodmont II and Corporate Boulevard.

The workshop brought together experts from throughout Europe to discuss specific considerations involved in clinical trial methodologies in small populations.

For the benefit of those unable to participate in the videoconference, CDER's Office of Training and Communications has posted the PowerPoint slides of the workshop agenda and presentations on the Center's intranet site at: http://cdernet.cder.fda.gov/dcm/Oct22.htm.

In addition, OTCOM has videotaped the proceedings, and the approximately 5-hour-long videotape is available at the main FDA Medical Library, Parklawn Room 11B-40 and at it's branch libraries in Woodmont II Room 3001 and Corporate Boulevard Room S-121.

A copy has also been sent to the CFSAN library.

FDA workshop participants found the workshop extremely valuable. Questions about accessing the materials should be addressed to me (FRIELJ) or **Pam Winbourne** (WINBOURNE).

John Friel is OTCOM's deputy director.

Microarray technology

(Continued from page 12)

molecules. They can be used to map the unique bits of our DNA that make each of us different without knowing the exact genes. Mapping these will be the next big project undertaken by the National Human Genome Research Institute (page 2).

Because proteins and antibodies bind together in pairs, microarray technology is being developed to measure proteins in context.

CDER public service announcements appear on Rx packages

(Continued from page 1)

to each medicine's unique National Drug Code and the patient's age and gender. So far, however, the division has been relying on its portfolio of messages aimed at wide audiences.

"We will soon begin working with other divisions in the Center to develop more specific messages," said **Ellen Shapiro,** the division's director.

One side of the tri-fold newsletter has three panels customized to the patient's age, gender and prescription:

- The first panel is the private industry prepared prescription drug information. The Center is evaluating the adequacy of this information under a 1996 law (July *Pike).*
- Another panel has health-related editorial matter.
- A final panel has a public service announcement or a paid drug company message. The Center's announcements only appear when there are no drug company messages.

When the pharmacy computer customizes the newsletter, it makes use of the National Drug Code. The code identifies the specific strength, dosage form and formulation of a drug product for a particular firm. The code for a drug to prevent and treat osteoporosis, for instance, may trigger osteoporosis health information. The code and a patient's age and gender could also trigger a Center message appropriate for senior women. The personal data for customizing remains with the pharmacy.

The second product is a similar tri-fold newsletter, except its content is generated from a generic drug's National Drug Code. The public service announcements in this program also include the three designed by CDER to increase consumer confidence in generic drugs (September-October *Pike).* This program is running in about half of the Health Resource retail pharmacy network.

The preprinted reverse side of both pharmacy newsletters contains items like store promotions and other announcements. Because the presence of the HHS and FDA logos on our announcements could be construed as an endorsement of the rest of the pharmacy newsletter content, the logos don't appear. The announcements do cite the Department and Agency as the source for the information.

The third product, a pilot running in 139 selected physicians' offices, currently uses four of our messages. At the end of an office visit, when the patient's diagnosis code is entered into the billing computer, a personalized newsletter is generated. The cover has the physician's office name, hours and contact information. The other three panels contain:

- Health information targeted to the patient's diagnosis, age and gender.
- A public service announcement from CDER suitable for the patient.
- General wellness information and recipes.

Because the physician newsletter contains no drug company ads or drug information, the public service announcement will contain the HHS and FDA logos and names, CDER's Web site and the 888-INFO-FDA phone number. So far, 10 Center messages have appeared, and three more have been approved for future use.

Cindi Fitzpatrick, a consumer safety officer in the Division of Public Affairs, is project manager for the Health Resource leveraging agreement.

McClellan emphasizes smart regulation in talks with employees

BY SHERUNDA LISTER

In two videoconferences for employees, new FDA Commissioner **Mark McClellan, M.D., Ph.D.,** discussed the concept of "smart regulation" and his three top priorities: homeland security, preventing medical error and providing better information to our constituents.

In the first videoconference, Dr. McClellan sat down in the Center for Devices and Radiological Health's studio and was interviewed by CDRH's **Mark Barnett.** In a second videoconference for CDER employees, Dr. McClellan spoke from Woodmont II and was introduced by Center Director **Janet Woodcock, M.D.**

"This is the most forward looking regulatory agency in the world," Dr. McClellan said in his CDER talk.

"I'd like to say that this is the most important job that I've ever had," he said in response to interviewer Barnett's first question about why he chose to take on the job of commissioner. "Promoting and protecting the health of the American public is surely up there at the top of the list on top government responsibilities."

Dr. McClellan explained that smart regulation is closely related to risk management. "The idea of smart regulation is to use all of the tools of the science of risk management and that other regulatory sciences have to offer to answer one of the key types of questions we face which is: 'How to protect and promote the health as efficiently as possible.'"

He urged Center employees to "think hard" about the review. "We have limited amounts of your time, money and regulatory authority," he said. He supports faster access to safe and effective treatments. That doesn't mean shorter review times, he said. He noted that early contacts between FDA and companies developing a drug led to faster times of approval and lower costs of approval. Smart regulation also includes getting the most out of each review cycle. Dr. McClellan looks to new technologies to increase the success rate of products or identify failing products early in development.

When asked about FDA's role in educating the public and health care professionals, Dr. McClellan said: "I think there is probably no higher priority in this agency than finding ways to reach our constituents more effectively with useful and relevant information. First and foremost on that list is the American public. For all that we do in terms of regulating new medical products and bringing valuable new treatments to the market—while those types of treatments have a tremendous impact on the public—they pale in comparison to what people can do for themselves through good health choices."

Medical errors are one of the country's top priorities, he said. "It has got to be a top priority of our Agency to help address these very common problems of avoidable complications, side effects, and

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