news along the pike

Center for Drug Evaluation and Research

Volume 2, Issue 10

Inside . . .

Fall Planning Meeting

Community, Collaboration, Cooperation, Communication

By Norman Oliver

Building community, fostering collaboration and cooperation, improving management and processes and implementing better communications were the broad goals for the Center announced at the Fall Planning Meeting by CDER Director **Janet Woodcock, M.D.,** and the Transformation Team.

Transformation Goals

Convert *staff* to *community*
united behind our mission
committed to a shared vision
living our operating principles.

Work *collaboratively* and *cooperatively*
with industry, academia and others
to improve the drug development
(regulatory system) and review process;
focus where need is the greatest.

Improve *management* and *processes*
by evaluating alignment
of processes and behaviors
with the mission, values
and operating principles;
where in alignment,
evaluate ways to improve;
if not aligned, refocus
and eliminate unnecessary work;
continuously improve.

Develop and *implement* a plan
to identify and integrate
new ***information*** management
and technology
into all activities:
internal and external communications
regulatory affairs
management.

"Ordinarily, I have given out short-term goals," Woodcock said. "This year we are announcing overarching goals. The transformation process is gathering up what the Center is doing and making sure it is working in concert."

Achieving the Center's goals should occur in the everyday jobs that people are doing, Woodcock said. To emphasize her point, the shorter term projects and objectives announced by her leadership team during the conference were explicitly tied to one or more of the goals.

The first goal, Woodcock explained, means that Center employees should be reaching out to others and that others should perceive us as a community. "One of the common perceptions is that, because we are so technical, we focus on our own work and not the overall goals. At some point, everyone must look at the big picture." Examples of how CDER is moving toward this goal include the scientific seminar series and the coordinating committee structure that brings people from all parts of the Center to work on policy issues. Woodcock said that her boss, Agency Deputy Commissioner for Operations, Michael A. Friedman, M.D., has charged her with having CDER take the lead in working more closely with the other centers and expanding the sense of community. Woodcock emphasized that all in CDER share a responsibility for thinking beyond their own organizational boundaries.

"We as a Center are responsible for the drug regulatory system," Woodcock said in prefacing her remarks on working collaboratively and cooperatively with industry, academia and others to improve the drug development and review process. "That is our responsibility to the people of this country." She explained that a newly formed consortium of leaders from

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Joe's Notebook

Fun with Chemistry

In one of my mad, machismo moments as an undergraduate, I signed up for chemistry. Of course, it was one of those old-fashioned schools in the days before you could meet the science requirements by taking Philosophy of Science for Liberal Arts Majors 101. So why chemistry? Well, my roommates were bragging about how they were going to take a popular chemistry course with the professor who actually wrote the book. "So, come on," they dared, "you can do it, too."

If you can call doing chemistry going in debt to the glass factory, putting psychedelic stains on your lab coat and creating insoluble messes on the lab bench, I suppose I did chemistry. Despite my fumble-fingered attempts at lab work, I did have one coup in the final *written* exam that I want to share with you, because this issue of the *Pike*, revitalized those memories from more than three decades ago. Our professor always tried to end his lecture with a practical example of the wonders of chemistry in everyday life. The example he used one day was soap. Washing your hands before eating or doing open heart surgery is one of the keys to preventing the spread of disease. This "miracle drug" was unknown until the Middle Ages. Ancient Romans had to build elaborate, three-staged baths to reap the public health benefits of cleanliness. Our professor's diagram of soap's reaction was nearly as complex as one of those ancient bath temples.

After a few minutes, only the hard core were still taking notes. We were in for a shock, however, when he asked us to describe the reaction for soap for 20 percent of the final exam grade. By this time, not only had I decided to major in English, I had learned from my math and physics courses that it was better to attempt any answer, hope for partial credit and rely on the magic of the bell curve. To this day, I recall the four words and three symbols I wrote: "Grease + soap + water = scum."

People who are now famous doctors and CEOs of biotechnology firms tried to diagram and connect all the molecular parts of this reaction. They did miserably on the question. There were only three in the class who received all 20 points. I was one. With full credit for one-fifth of the final and the bell curve in my hip pocket, I did surprisingly well in my brief fling with a real chemistry course. It was also one of those epiphanous experiences that made me decide I was a big picture kind of person.

"At some point," I quote **Janet Woodcock** in the lead story, "everyone must look at the big picture." In this issue you can go from global on pages 4 and 5, to Agencywide on page 9, to CDER in our coverage of the Fall Planning Meeting and to all the parts and people that make it happen in our Corners and People Along the Pike. Some of the big picture comes from reports on the weekly scientific seminar sponsored by the Center's Coordinating Committee for Advanced Scientific Education and usually emceed by *Pike* contributor **Zan Fleming.**

It's still fun with chemistry, the thrill of discovery, and their contributions to public health that bring us together as a community in CDER. Converting staff to community is our Number One transformation goal. I hope you feel that sense of community when you read **David B. Katague's** appreciation of his colleague, **B. Vithal Shetty,** on page 10; share the pride of accomplishment of **Jack Pevenstein** and **Xavier Ysern** on page 11; or see how a group comes together and forms a team to solve a particularly pressing problem in **Edward Miracco's** account on page 4.

Finally, it's not the same as being there, but it's a better deal than renting a Hollywood thriller from the video store or reading my summaries in the *Pike.* You can check out the videos of CDER's scientific seminars from the Medical Library.

And the winner of lunch along the *Pike* for last month's contest to eliminate the hairline in the logo is **Noreen Gomez** from the Office of Management. The hairline is still there, but not for want of an imaginative suggestion from Noreen.

news along the pike

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

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Please contact a member of the Editorial Board or:

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Ombudsman's Corner

CDER Transformation in Full Bloom

By Jim Morrison

So often we are too close to the trees that we miss seeing the forest. An excellent example of that cliché is CDER's transformation process. In my job as ombudsman, I see plenty of trees, in the form of calls, e-mail and letters, mostly complaining about what is wrong with our systems and people's behavior. I believe it is essential that I periodically take the time to step back from the trees and view the broader landscape.

One such opportunity came in the form of the Fall Planning Meeting (see coverage beginning on page 1). It was a marathon event lasting some 10 hours, but those of us who managed to sit through all the presentations were rewarded with a view of the Center that revealed some remarkable changes since the previous sessions. Incidentally, if you missed the live presentation, shortly there will be tapes of the sessions available through the library.

A lot has happened in the past six months to change CDER's outlook. It was only in March that CDER's senior managers first got together during a go-away to form the Change Team and drafted CDER's mission, vision and values statements. Since that time, the Change Team has begun to function cohesively, working together toward commonly set goals. If you compare the presentations at the fall planning sessions to those in the spring, you will see much more attention was paid to how the goals for each office align with those of the Center, and you will see many more references to cross-organizational activities.

Without much fanfare, CDER has moved from the initial phase of its transformation, that of establishing its vision, mission and values, to setting its goals and getting down to the nuts-and-bolts work of seeking results based on the broad goals. Currently, the Change Team, augmented by the Leadership Fellows, has identified six general results and specific projects and actions to accomplish those results. The results are:

- A highly satisfied, productive and efficient CDER staff.
- Improved efficiency of the drug regulatory system.
- Improved quality and timeliness of drug development and review.
- Expanded international harmonization.
- Improved communication of essential drug information to consumers, patients and health professionals.
- Increased internal and external awareness of CDER's work and the value it adds to society.

The working groups have met and will meet again Nov. 20. As the planning for these results efforts becomes firmer, additional people from throughout CDER will be recruited to help. If you want to be a part of this transformation process, and I certainly recommend that you do, keep watching your e-mail, the *Pike* and the new CDERnet for more information.

Speaking of the CDERnet, which was unveiled Nov. 5 (reachable by typing "www" in the address box for those of you with Microsoft Internet Explorer), that intranet site and CDER's Internet Web site are further evidence of the Center's transformation. I can personally attest to the power of the Internet in expanding communications. Since my Ombudsman page went on-line last month, calls, letters and e-mail to me from outside have tripled. Not only am I getting more industry complaints and suggestions, but I am also getting questions and requests for assistance from consumers, patients and health professionals. Progress has a price, but I am enjoying the challenge.

Jim Morrison is the Center's Ombudsman.

Mentor's Corner

CDER's Medical Library Source for Books on Mentoring

By June Cory

There are six mentoring books located in our CDER Medical Library. They are on the shelf in the management section of the Parklawn Library in 11B-40, and the satellite libraries can get a copy if you are located in other buildings. Here are the books, listed alphabetically by author, along with the library's call number:

Chip R. Bell, 1996, *Managers as Mentors: Building Partnerships for Learning,* San Francisco: Berrett-Koehler Publishers, HF5385.B45.

John P. Fernandez, 1991, *Managing a Diverse Work Force: Regaining the Competitive Edge,* Lexington, Mass.: Lexington Books, HF5549.5.M3F467.

Marna A. Owen, 1991, *Beyond the Myths and Magic of Mentoring: How To Facilitate an Effective Mentoring Program,* San Francisco: Jossey-Bass Publishers, HF5386.M8575.

Gordon F. Shea, 1992, *Mentoring, a Practical Guide,* Los Altos, Calif.: Crisp Publications, HF5385.S54.

Marie A. Wunsch, 1994, *Mentoring Revisited: Making an Impact on Individuals and Institutions,* San Francisco: Jossey-Bass, LB1731.4.M46. Copies of this book are also in the Woodmont and Corporate satellite libraries.

Michael G. Zey, 1991, *The Mentor Connection: Strategic Alliances in Corporate Life,* New Brunswick, N.J.: Transaction Publishers, HF5386.249.

June Cory is a chemist in OTCOM's Division of Training & Development.

Office of Compliance

Focus on Certificates to Foreign Governments

By Edward Miracco

The months of July, August and September saw the Division of Labeling and Non-Prescription Drug Compliance in the Office of Compliance focus most of its resources on one project: the issuance of Certificates to Foreign Governments. These certificates, also known as Certificates of Free Sale or Certificates of Pharmaceutical Products, declare that the manufacturer of a particular drug product is subject to periodic inspection by FDA. They further state that the most recent inspection showed that the manufacturing facility complied with the Good Manufacturing Practices (GMPs) for drugs. Many foreign governments require this documentation before they allow a foreign manufacturer, including a U.S. manufacturer, to export drug products to their country. FDA generally receives the request from the manufacturer.

Requests for the certificates, called "certs" for the sake of brevity and verbal efficiency by those who work with them, come streaming in, packaged in boxes, bags and envelopes, to the tune of approximately 400 per month. Because of the overwhelming quantities and the resource limitations and compliance priorities in the division, the certs began to backlog. At one point, in July, the division had almost 2,600 awaiting processing. This processing requires a time-consuming array of steps to assure that the finished product is correct in all details. These steps include: computer logging the arrival; assuring the submission is complete; checking the GMP status of the manufacturing facility; typing; double-checking for accuracy; signing; notarizing; applying the gold seal and imprinting with the official Department of Health and Human Services insignia; in some special instances, affixing red ribbons to the documents through grommets; and, finally, putting the completed certs in envelopes for mailing.

During the months of intensified cert processing, several modifications to the procedures were implemented. These changes served to increase efficiency, reduce duplication and generally accelerate all handling steps. For example, one simple modification, utilizing self-adhesive gold seals rather than those that require moistening, saved a great deal of time. It also made the processing less messy. Division meetings held twice weekly were also instrumental in communicating other processing modifications and, as general information-sharing sessions, to improve efficiency further. The division has recently obtained its own postal meter to decrease in-house time even more, and the Office of Compliance has allocated additional resources to the program. Additionally, modifications to the type of information included in the certs have been made. With the improvements to the process, added resources and changes in the program, the issuance of certs should be kept on track in spite of their inexorable flow into the Office of Compliance.

After the dust had settled, it was clear that the division had come through with flying colors. The backlog had been eliminated in an extended frenzy of activity that witnessed each and every CSO, technician and secretary playing a major role. It was a classic demonstration of teamwork and cooperation by everyone, including three individuals participating in the FDA Leadership Development Program and several others normally assigned to other divisions. Although all participated greatly, special recognition is deserved by the three select members of the Division of Labeling and Non-Prescription Drug Compliance staff who coordinated the effort, assured the continuity and flow of each processing step and who were always available for guidance. These individuals, **Jocelyn Lewis, Roxana Fay** and **James Hamilton,** spent many weekends and evenings eating, drinking and sleeping certs, even voluntarily postponing their own leave when necessary. Their dedication to the project directly correlates to its successful conclusion and is a tribute to their professionalism.

Edward Miracco is a CSO in OC's Division of Labeling and Non-Prescription Drug Compliance and was a member of the "Cert Team."

Effective Regs Support Industry

By Norman Oliver

Effective regulation is one of three legs of a stool that provide key support to the research-based drug industry around the world, according to Dr. Harvey E. Bale, Jr., Senior Vice President, International Affairs, Pharmaceutical Research and Manufacturers of America (PhRMA). During a presentation at CDER's scientific seminar series, Bale placed the Center's role in drug regulation in a global perspective.

In some parts of the world, Bale said, "We wish we had an FDA." Counterfeit and adulterated drugs can pose major health hazards in countries that don't effectively regulate their drug industries.

"Without an FDA, you have a Gresham's law in which bad products drive out the good."

Bale is a political economist and worked for the U.S. International Trade Representative before joining PhRMA. He identified the three legs of support for the pharmaceutical industry as:

- Protection of intellectual property.
- Effective product registration and enforcement.
- Economic policy as it relates to health care.

"These are the core issues for a large pharmaceutical firm. Product registration is absolutely vital," Bale said. "Failure on

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EEO Corner

Celebrating National Disability Awareness Month

By Gloria Sundaresan

CDER joined the FDA Equal Employment Opportunity and Civil Rights Office in the observance of the National Disability Awareness Month on Oct. 30. The speakers were Dick Sheppard of the President's Committee on Employment of People with Disabilities and Dr. Charles H. McNelly, Executive Director of United Cerebral Palsy Foundation. **David Feigal, M.D.,** Acting Director of the Office of Drug Evaluation IV delivered the opening remarks.

Dr. Feigal recalled that when he first came to FDA, he spoke at the all-hands Anti-Viral Division meeting and did so with the help of a sign language interpreter. This was done specifically for a valuable technical staff member who was hearing impaired.

He also mentioned that this was the first time he had become aware of a workplace that made adjustments to accommodate employees with disabilities.

As a result of this, sign language was taught on-site for the division's employees. Over the years, two other employees with disabilities joined the Anti-Viral Division. Dr. Feigal pointed out that he was proud of the policy and the commitment of the Agency and the Center in giving opportunities to disabled employees. Dr. Feigal also cited Joseph Campbell's observation in *The Power of Myth* that the different religions in the world frequently come up with the theme that appears to say that we are all interconnected, one to each other, all of us with responsibilities for each other, all of us together. Dr. Feigal ended his remarks by paraphrasing Bill Moyer's comment on Campbell's observation on interconnectiveness: "We care for our neighbors because we are our neighbors."

Seize the Day Performers in wheelchairs presented a performance to a samba tune by Brave Combo. Instead of the fast and fancy footsteps in dancing the tango, the audience was awed by the rolling, quick stopping, whirling and twirling of the wheelchair dancers. It was simply delightful and another eye-opener to what persons with disabilities can do.

When the audience was invited to participate, **Guyann Toliver,** from the Division of Neuropharmacological Drug Products and CDER's representative for disabled employees, answered the call and danced the polka with the rest of the Seize the Day Performers and other volunteers in the audience.

On Nov. 13, CDER's EEO Office participated in the Montgomery County Government's celebration of Diversity Day in Rockville. The event was observed with programs, information exhibits, arts and crafts, cultural entertainment, and ethnic and international foods. CDER's EEO Staff set up an information booth with materials about foods, drugs, health and other consumer concerns. We also provided recruitment packages and a list of vacancies in the Center as well as the FDA.

Gloria Sundaresan is a member of the EEO Staff.

New Drugs Rely on Regulation, Protection, Policy

(Continued from page 4)

any one of the three legs of the stool can make the stool tip over and fall. If one of them breaks, the whole system breaks."

Product registration protects a company's investment in researching and developing a new drug. Bale pointed out that the companies his organization represents are in a high-risk business in which only one in 5,000 chemical entities synthesized ends up approved by the FDA. The major markets for new drugs are North America, Japan and Europe.

Since the Prescription Drug User Fee Act (PDUFA), review times have decreased. The major time is in clinical development.

The United States is responsible for about one half of the new chemical entities globally, and protection of intellectual property provides a manufacturer with time to recoup costs of developing a product. "The pharmaceutical industry is the industry most dependent on patent protection," Bale said.

Without government protection of patents as well as trademarks and trade secrets, other firms would counterfeit a drug or market a generic version before a firm realized a profit on its investment. Without the profit incentive, firms would not invest in drug development.

Bale discussed how poor countries, who have weak protections for intellectual property protection, argue that their policies allow their citizens access to new drugs while having the development process supported by rich countries.

Bale countered that many countries that follow this policy face a different array of health problems than in more developed countries, and their policies discourage their own scientists and entrepreneurs from developing medicines that address their public health needs.

Economic policies can promote or hinder the development of new drugs. Countries that place price controls on drugs, in an effort to lower the cost of health care, can impair the development or marketing of new drugs within their borders, Bale said. Prices set too low can undercut the financial incentives drug innovation requires.

AMF Corner

Division Files Management System Moves to New Tool

By David Isom

In the April 1996 edition of the Pike, we provided an overview of the many components of the Automated Files Management (AMF) project. In the issues that followed, we highlighted the computer-searchable storage of an entire division's files for the Office of Clinical Pharmacology and Biopharmaceutics (June), the Approved Package Insert Repository (July), the Decision Support System (May and August), and the Electronic Charge and History Card (October). The remaining components include the Division Files Document Management System (DFDMS), and the supporting cross-component efforts such as training, documentation and Windows programming.

The goal of the DFDMS component is to develop a CDERwide document management system to improve the way the Center archives, tracks and retrieves all the documents generated during the review process. With the CDER goal to move toward a paperless review paradigm, the Division Files Document Management System must include capturing signatures and other elements so that the archived electronic documents can serve as the source documents for Freedom of Information requests and other reference needs.

We had reported in April that the Division of Oncology Drug Products was serving as the DFDMS development user and pilot group. With their help, the DFDMS team documented the work flow through a review division, the Oncology Division's specific document management requirements, and the prototype design for a pilot. Unfortunately, the team had to conclude in August that the tool originally selected to pilot the system would not meet CDER's needs.

After evaluating the product information and literature of several groupware and document management tools on the market, as well as comparing the capabilities of these tools with the requirements of the DFDMS, the development team selected Documentum for the next pilot.

This tool selection is based on the requirements developed in Oncology, the archiving requirements of the Center and the tools used in other parts of FDA and in the marketplace and, particularly, the pharmaceutical industry. Although the other products in the tool evaluation did meet many of the specific requirements of DFDMS, Documentum provides more "off-the-shelf" workflow, signature and management information systems integration capabilities, as well as the scalability and management of large compound documents that we require.

The transition to a new tool will require a delay in starting a pilot in the Oncology Division. However, the initial development work in that division is making the transition to a new tool much easier. A major part of this transition will involve the design and implementation of the prototype requirements in the new tool. The team plans to restart the Oncology pilot in early 1997.

David Isom is the AMF project manager.

Project Management Corner: Templates Anyone?

By Susan Cusack

I'm sure that there are a variety of project management methods used throughout the Center. I know one CSO who organizes his life and projects with five calendars. My hat is off to that. At any given time, I am not likely to know what day it is. If I had to make five calendars merge, someone would probably find me in the corner counting my toes. I prefer to use Microsoft Project; it knows what day it is, so I don't have to.

In a project management course that I attended recently, the instructor surveyed the class to find out what project management software was used in the Center. The unanimous answer was Microsoft Project. In discussions with the other attendees, I learned that while the software is available to most of us, the use of it ranges from "not at all" to "life would come to a crashing halt without it."

As most of you know, there are courses offered through the Parklawn Training Center on how to use Microsoft Project. These are great courses if you need to learn how to use the software. The chief complaint that I have heard is that Microsoft Project is a typical business application that doesn't exactly capture what we do. Therefore, knowing how to use it doesn't necessarily help a new user customize it to the drug review process and it can be discouraging.

Take heart, there are CSOs and project managers who have customized it and created templates. My peers and I, in Medical Imaging, have templates under construction and I'm sure there are others. If you would like to share yours or try mine and offer feedback, please notify me (e-mail: CUSACKS). If I get any response, there will be a future column describing the available templates and we will put them on the x:drive for easy access.

Last month this column was heralded as an information exchange for CSOs and project managers. Please send me an e-mail with any information that you would like to share. At the request of a reader, next month's column will focus on minute taking. If you have any comments, questions or helpful hints, please send me an e-mail message.

Susan Cusack is a consumer safety officer in ODE III's Division of Medical Imaging and Radiopharmaceutical Drug Products.

Reviewers' Corner

Coming Soon to a Screen Near You . . . the Virtual Journal

By Zan Fleming

Imagine that you are "flexiplacing" at home, working on the review of a Kaplan-Meir plot, and come across the term, "stochastic curtailment." You are a little hazy on what s.c. means so, at your computer screen, you click on the icon for CDER's virtual *Journal of Drug Evaluation.* An attractive menu pops up and gives you the choice of seeing the current edition's table of contents, word/term searching the entire contents or going to the cumulative index. Clicking on the index gives you a choice of surfing the index or typing in a word or term. By the time you have punched in the first four letters—Boom!—stochastic curtailment pops up. Selecting it brings up the titles, dates and authors of eight entries, the first one designated as a review article. Click on that article, and the title page immediately pops up. After reading the abstract, you have everything you needed on s.c. within a couple of minutes, but you say to yourself, "Hmmmm, this is pretty interesting." Four hours later, after going from one linked article to another and ending up in a piece on the drug regulatory system of Russia, you say: "Maybe I better get back to work. Let's see; I was at that curtailment thing."

Refraining from extended surfing after going to the virtual *Journal of Drug Evaluation* (vJDE) for help during a review may, at least in the beginning, be one of the biggest problems for reviewers. This new tool for reviewing, learning and scientific community building is not only going to be irresistibly useful and easy to use, but it is also going to be fun. We are at least a few months away from that vision, but it is coming sooner that you might imagine. In September, Janet Woodcock appointed both executive and editorial boards for the journal. Both groups have met jointly and separately several times. Much has been accomplished, but many important details remain to be settled, ranging from the need to protect confidential information to whether articles will be published as they are accepted or grouped into conventional volumes and released weekly or monthly. A firm target date for publication of the first issue has been set for this January.

The idea of a virtual journal began very modestly. It was a response to the need for an easy and inexpensive way to capture and organize the huge intellectual yield of CDER professionals and make this information and wisdom easily accessible to reviewers. We are starting to understand, however, the unlimited potential of this medium. The use of "Internet-like" technology will make the printed journal medium obsolete or at least less used than the electronic version. For example, there is no need to be bound by the usual constraints of conventional publishing such as limitations on number and length of articles. All submissions that meet the editorial standard can be accepted. Other advantages include a table of contents that can be individually customized by the user, for example, a reviewer could specify a table of contents with only pharmtox articles. To speed retrieval of desired information without having to scroll whole articles, abstracts will serve as the primary access points for the readers. Hypertext links will largely supersede the conventional bibliography and will aid the reviewer in finding additional information, in or outside the CDER intranet, more quickly. A search engine feature will make the entire body of knowledge accumulated in the journal easily retrievable. Because of the nature of the electronic medium, text and figures can be easily imported and incorporated into reviews.

The journal will consist of several different sections: full-length, peer-reviewed articles; case studies; articles on regulatory philosophy and organizational/review process issues; letters to the editor; and "the Workshop."

The vJDE is currently planned, for the time being, to be used by and contain only the work of CDER employees. It is envisioned that the Journal will eventually have an international version that is simply the internal version from which sensitive information has been removed. The journal, likewise, could include appropriate submissions from any writer in industry, academia or other regulatory authority. As its readership and source of articles expands beyond CDER, the good principles and practices of drug evaluation will become understood, utilized and continuously evolved by all who participate in the development and evaluation of therapeutic agents. Ultimately, however, the vJDE will always be for and by the CDER reviewer.

The journal will consist of several different sections: full-length, peer-reviewed articles; case studies; articles on regulatory philosophy and organizational/review process issues; letters to the editor; and "the Workshop." This final section will allow the early appearance of articles in draft and preliminary communications. Possibly to be included is a "chat room." Every seasoned CDER reviewer already has experience that can be incorporated into publishable articles. We hope you will make suggestions to us or any of the other board members about developing the journal. We also urge you to start thinking about your first article for the vJDE.

Zan Fleming is a group leader in ODE II's Division of Metabolic and Endocrine Drug Products.

Pediatrics Corner

Improved Pediatric Labeling Moves Ahead

By L. Miriam Pina, M.D.

As many of us know, the new Pediatric Rule, published in December 1994, was the result of a Centerwide initiative directed at improving the pediatric information in the drug label. This rule states that once the FDA decides that the course of a disease and the effects of the drug are sufficiently similar between adults and children, the sponsors may use extrapolated efficacy data from clinical studies conducted in adults and other pediatric supporting information, i.e., dosing and safety data, as the basis for labeling the drug for use in the pediatric population.

The Final Rule requests that sponsors submit a pediatric use supplement within two years by December 1996. "If the FDA concludes that a particular drug is widely used, represents a safety hazard, or is therapeutically important in the pediatric population, and the drug sponsor has not submitted any pediatric use information, then the agency may require that the sponsor develop and/or submit pediatric information," the rule states.

After the Final Pediatric Rule was published, the Pediatric Subcommittee created 10 working groups to implement it. One of these, the Pediatric Use Survey Working Group, identified the drugs most widely used off label in pediatrics. The group reviewed a 1994 commercial database and identified the drugs most commonly prescribed off label in the pediatric population. The working group is currently preparing a manuscript to publish the data in a medical journal. Meanwhile, the Agency has contacted the sponsors of these drug products and requested that they submit adequate pediatric data to improve the pediatric use information in the labels.

Members of the Pediatric Use Survey Working Group are: **L. Miriam Pina, M.D.,** chair, Division of Pulmonary Drug Products; **Kimberly Struble,** Division of Anti-Viral Drug Products; **Linda Hu,** Division of Over the Counter Drug Products; **Jonca Bull, M.D.,** Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products; **Cazimiro Martin,** Division of Over the Counter Drug Products; **Frank Rosa,** recently retired from the Division of Pharmacovigilance and Epidemiology; and **Charles Maynard,** Division of Pharmacovigilance and Epidemiology.

L. Miriam Pina, M.D., is a visiting scientist in ODE II's Division of Pulmonary Drug Products

DHHS News to Note

Policy on Informed Consent & Emergency Therapies Issued

The Food and Drug Administration and the National Institutes of Health announced last month measures designed to protect individuals who may benefit from experimental treatments in life-threatening emergencies.

The FDA issued final rules to make it easier for promising experimental drugs and medical devices to be studied in persons who are in life-threatening situations and unable to give informed consent for their use. As a companion document, NIH has published "Emergency Research Consent Waiver" applicable to all agencies of the Department of Health and Human Services.

These policies establish narrow limits for allowing research without informed consent in certain studies of emergency medical procedures and harmonize these standards throughout the Department. **Carolyn L. Hommel,** a CSO with the Division of Scientific Investigations, Office of Compliance, is currently drafting the Center's MAPP on the new policies.

Under the new conditions, patients could be enrolled in clinical trials without their consent, provided that an independent physician and an institutional review board (IRB) of experts and lay persons agree that:

- The clinical trial addresses a life-threatening situation and that other available treatments are unproven or unsatisfactory.
- The research cannot practicably be carried out otherwise.
- It is not feasible to obtain informed consent from the patient or the patient's legal representative.

In addition, the risks and benefits of the experimental procedure must be reasonable compared to those associated with the patient's medical condition and standard therapy.

Vital Statistics Report Shows Broad Gains in Nation's Health

The Centers for Disease Control and Prevention released annual preliminary vital statistics findings for 1995 showing broad gains in national health indicators. According to the report, "Births and Deaths for 1995," prepared by the National Center for Health Statistics, the United States last year achieved an historic low infant mortality rate, a continued increase in the number of women obtaining early pre-natal care, the first decline in the birth rate for unmarried women in almost 20 years, a continued decline in the teen birth rate, a leveling in the HIV/AIDS death rate for the first time since the epidemic took hold, a dramatic decline in homicide rates, and a continued increase in life expectancy.

FDA's Office of Women's Health Now on Internet

The Office of Women's Health has information available now pertaining to food, nutrition and cosmetics on its Web site. Expansion is planned in the not too distant future to include information across the broad range of product areas within FDA's jurisdiction, including drugs, devices and biologics. To access the site from the FDA home page, click on the "Foods" icon, then on "Women's Health."

Limited Dollars, Great Science, High Expectations

Friedman Outlines Agency Priorities

By Norman Oliver

Continuing constraint on resources, expanding base of scientific discovery and rising expectations for improved FDA performance will shape the Agency's work in the foreseeable future, according to **Michael A. Friedman, M.D.,** Deputy Commissioner for Operations. Friedman outlined the impact of these broad forces at a recent CDER scientific seminar. "We have more to do than we can do. How well we choose what we focus on is a very important responsibility, and it is a particularly difficult task. The challenge is to look ahead and decide what the most important, major public health issues will be."

While portions of CDER benefit from the Prescription Drug User Fee Act (PDUFA), reductions in appropriated funds to the Agency are going to continue to have an impact on everyone, Friedman said. "We can't wait for more resources, or people, or more space because they probably won't come," he said.

"We need to recognize how driven we are as an Agency to perform at the highest level," Friedman continued. "I am not sure that people can work harder than they already do. I do, however, believe that people can work more efficiently." While pointing out that he has little facility with computers, Friedman said that one route to improved efficiency is for the Agency to make better use of information technology including the Internet and intranet systems.

"The shear breadth of scientific discovery is going to expand. Our challenge is incredibly complex and is going to get more so," Friedman said. "How can we effectively deal with new science? We need to improve our FDA laboratory science in mission relevant applied and basic research," said Friedman, who came to the FDA from the National Institutes of Health. Friedman set a personal priority to focus on helping determine the best use of the laboratories and the scientific expertise of the Agency. "There is a vast and growing amount of scientific knowledge. We don't have all the requisite skills in the Agency. We have to think of creative ways of gaining those insights."

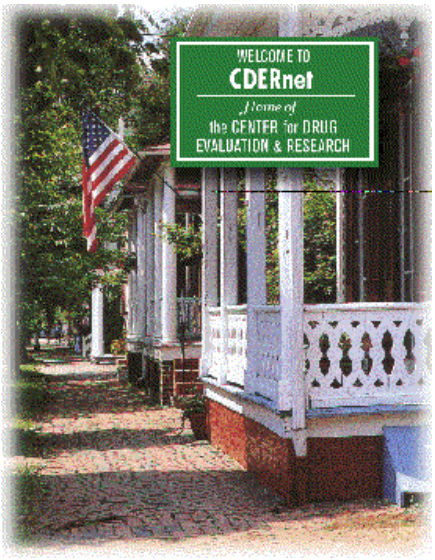
Rising expectations about what the Agency can do for the public health of Americans are entirely predictable, Friedman said. "Our own expectations dwarf even those of our harshest critics," Friedman said. For CDER, Friedman stressed that high expectations will emphasize the review and approval of new products. "The performance of that function as defined by PDUFA should be a source of enormous pride," Friedman stated. "You have set the expectation that the Agency will perform well against the most stringent set of objectives. You have reviewed a large number of new products and achieved a really splendid record for the past year. The question will be: Can we deliver even more in the future?"

Reviewing new products calls for multiple decisions, according to Friedman, and the Agency tries to make them correctly. However, what appears right for a reviewer may not be viewed in the same light by a patient. "Now, we attempt to provide both judgment and information about products we approve," he said. "In some instances people appreciate that. But the community of patients might set their comfort point at a different level than reviewers. I think our role as an information agency is increasing."

Another challenge facing the Agency is to take better advantage of biological diversity among humans. "At some point in the future, we would like to say that a certain product works well in a certain patient with a certain biological profile," Friedman said. For common profiles, current science works fairly well, but for uncommon types it doesn't always do so. "We need to evolve to some higher form of information that allows the patient, physician or insurer to make practical decisions."

Friedman recognized that internal changes that improve Agency operations are essential. "The speed and results of the change must be paid attention to," he said. The best change, Friedman noted, was the kind that bubbles up from the individual centers.

CDERnet Makes Debut



On Nov. 5, CDER launched an intranet for the exclusive use of its employees. With a Web browser on a Center computer you can visit the site by typing **www** in the address block. Ultimately, the CDERnet will allow access to Center databases through a user friendly Windows interface and the linking together of data from a variety of sources. Webconferencing will permit on-line discussions in an easy to follow format.

Chemistry Reviewer Still in Lab

Discovers Potential New Route to AIDS Treatment

By David B. Katague, Ph.D.

It seems that very few people know about a quiet, dynamic and creative genius among us. In spite of his deep involvement in the drug review and approval process as a primary chemistry reviewer for the Office of New Drug Chemistry III, collocated in ODE IV's Division of Anti-Infective Drug Products, **Dr. B. Vithal Shetty** devotes the rest of his time to research at the National Institutes of Health. Under a professional development (PD) arrangement approved by the division, Dr. Shetty works on developing a new method of attacking the virus that causes AIDS. Dr. Shetty's training is in medicinal chemistry, pharmacology and pharmacy. He obtained his B.S., M.S. and Ph.D. degrees from the Philadelphia College of Pharmacy and Science and is a pharmacologist by training.

Dr. Shetty has spent a major part of his career in drug research, discovery and development in the pharmaceutical industry in the United States. While in private industry, he organized and managed a multimillion dollar drug research and development center for a large pharmaceutical company in Rochester, N.Y.

Some of his major FDA accomplishments include serving as an expert witness in a price-fixing case and showing how a widely used drug could be manufactured with greater purity. The first case involved two well-known diuretic drugs. The firms had argued that because of complex manufacturing procedures, they had to charge higher prices. Dr. Shetty successfully showed that the manufacturing process was so simple that a high school chemistry student could be trained to make the drug in the laboratory. The case was settled out of court.

In a second case, Vithal was asked to examine an approved drug which was widely used for ulcerative colitis, but was only 80 percent pure. The firm had been arguing that, because of the lack of technology, it was not possible to purify the drug further even though the impurities were toxic. After a detailed investigation of the methods used to synthesize the drug, Dr. Shetty showed how it was possible to use existing technology to obtain 95 to 98 percent purity. On the basis of his recommendation, the firm was asked to come up with a drug at least 95 percent pure. The firm has since complied.

Dr. Shetty is the discoverer of the well-known drug metolazone, a diuretic widely used for the treatment of congestive heart failure and high blood pressure. He is one of the early pioneers in sustained release drugs and worked on a sustained release version of phentermine resin that is used to treat obesity. Dr. Shetty has numerous U.S. and worldwide patents as well as publications in peer-reviewed journals.

Vithal's current research at NIH involves the discovery of a new class of compounds and their development as potential treatments for AIDS. He has already been issued a patent for his findings on the bis-adamantanamine compounds, which have antimicrobial and antiviral properties. The patent has been assigned to the U.S. Government. This class of compounds has been found to have multifunctional activities. Dr. Shetty states that these molecules can be rationally designed to target viruses such as HIV and herpes which have an outer coat similar to that found in normal cell walls. The new molecule, he feels, has given him a definite lead in the race to discover a cure for AIDS. He is forthright in stating that he does not want to come up with another drug, like AZT or the protease inhibitors, which only delays progression of the disease. His dream is to find a total cure for this devastating disease. Vithal says, "No virus, no disease."

The structural features of his molecule provide a novel mechanism for killing the virus. One portion of the molecule is highly toxic, and another portion binds to cell walls and to the viral coatings. Vithal's highly focused and relentless pursuit of his research at NIH, includes work on altering the structure of his molecule to increase its antiviral activity and decrease its toxicity to host cells. In theory, it should be possible to make the portion that attaches to the viral wall more specific to the virus and less likely to attach to and harm normal cells.

"Work is thy right, fruit thereof, is not yours."

In the laboratory, *in-vitro* studies have shown that these molecules so far have been found to have potent activity against viruses like HIV, gram-positive and gram-negative bacteria, fungi, yeasts and amoebae. This is exactly what Dr. Shetty wants in his ideal molecule, since these combined activities are extremely useful in treating opportunistic infections in profoundly immunocompromised patients. He said he will leave no stone unturned until he finds a cure for AIDS. Dr. Shetty's bis-adamantanamine molecule is already being investigated by various pharmaceutical companies. One company, in particular, is very excited in developing it as a major antimicrobial drug with a wide spectrum of activity.

It is interesting to note that this highly talented and energetic scientist had to be coaxed to agree to my writing a brief story about his pioneering research work on AIDS. Vithal says that this is because of his strong belief in an Indian philosophical dictum: "Work is thy right, fruit thereof, is not yours."

David B. Katague, Ph.D., is a review chemist with the Division of New Drug Chemistry, collocated with ODE IV's Division of Anti-Infective Drug Products.

People Along the Pike

DHHS Employee of the Month

Secretary of Health and Human Services **Donna E. Shalala** named **Jack Pevenstein,** a project manager from the Division of Biometrics III, as the Department's employee of the month for September. "It's nice to receive the award when you enjoy what you are doing," Jack said shortly after the ceremony during the CDER office directors' meeting. "I like to create things. I am a perpetual student, and this job keeps me fired up."

Jack, who only joined CDER six years ago, was cited for a host of contributions to the Center and to the Division of

From left, Robert O'Neill, Director of the the Office of Epidemiology and Biostatistics, Jack Pevenstein, DHHS Employee of the Month for September, and Center Director Janet Woodcock display the letter from DHHS Secretary Donna Shalala announcing the selection.

Biometrics III in the Office of Epidemiology and Biostatistics. Among his contributions to CDER are his efforts in education, in particular his assistance in the development of a comprehensive plan for the education of new reviewers and his work on the advisory committees formed by the formation of the Office of Training and Communications. Jack is a retired Prince Georges Country elementary school principal.

New RAPS Award Honor's Webmaster's Father

The Leonard Stauffer Award, named in honor of CDER Webmaster **Paul Stauffer's** father who died last year, was announced by the Regulatory Affairs Professionals Society (RAPS) at its 20th annual convention in September. The first of the annual awards, established by the society's Regulatory Affairs Certification Board, was presented posthumously to Leonard Stauffer and accepted by his wife, Anne. The award recognizes Stauffer's ground-breaking role in implementing the RAPS certification program.

CDER Chemist's Discovery Published in *Nature*

Xavier Ysern, a review chemist collocated with the Division of Metabolic and Endocrine Drug Products, couldn't contain his excitement when he stopped by my office on Nov. 14 carrying a printout of the World Wide Web index to the just-published *Nature*. Certainly, one of the defining events in any scientist's career is to have his or her research published in one of the world's leading interdisciplinary scientific journals. Publication in a journal such as *Nature* indicates the finding has broad significance.

So, if you're a "structure maven" as Stanford University's Peter Parham dubs devotees of this type of chemistry in his "News and Views" review of the discovery, then be sure to check out "Crystal Structure of a T-Cell Receptor β-Chain Complexed with a Superantigen" in the Nov. 14 *Nature*, volume 384, pages 188-192, by Barry A. Fields, Emilio L. Maichiodi, Hongmin Li, Xavier Ysern, Cynthia V. Stauffacher, Patrick M. Schlevert, Claus Karjaiainen and Roy A. Mariuzza. Xavier's contributions to the investigation took place under a professional development arrangement at Roy Mariuzza's lab at the University of Maryland's Center for Advanced Research in Biotechnology (CARB) in Rockville.

Xavier and his colleagues have described an important molecular clue that may lead to the rational development of therapies for food poisoning and toxic shock syndrome. For acute cases, there is, as Xavier points out, only supportive and palliative therapy. Superantigens are viral or bacterial proteins that trick the human immune system into triggering the production of huge populations of T-cells and have been implicated in diseases such as diabetes mellitus and multiple sclerosis. The group at CARB has provided a three-dimensional picture that improves understanding of how these superantigens sabotage the human immune system.

Native Americans Working in CDER

The Office of Management's **Noreen Gomez** writes to remind me that November is Native American and Alaskan Native Heritage Month. The Center salutes six of its employees who represent two of 504 native tribes recognized by the U.S. Government. Descendants of the Cherokee Nation are **Sharon Brownewell, Millard C. West, Jr.,** and **Hartsell L. Whitacre, Jr.,** all from the Office of Management; **Angela M. Youngblood,** Office of Training and Communications; and **Helen N. Winkle**, Office of Testing and Research. **Tawni M. Brice,** Office of Compliance, is a descendent of the Alaskan/Aleut tribe.

—Joe Oliver

Fall Planning Meeting

Community, Collaboration, Cooperation, Communication

(Continued from page 1)

government, academia and industry is focusing on system changes that will speed the development of new medicines. Woodcock cited a number of Center initiatives designed to improve and streamline the review process for new and generic drugs, expedite pre-approval inspections and enhance post-marketing surveillance.

Setting goals for people, Woodcock emphasized, is the key to improving the Center's management and processes and aligning behaviors with CDER's mission, vision and operating principles. Tools to help achieve the third goal include the new employee performance plan and the just completed organizational effectiveness survey. Personal skills include listening better and working in teams.

As an example of improved management of processes, Woodcock cited the budget process: "We have gone from a chaotic management of our budget to one that is open and in which everyone knows where the money is going," she said. "This was a tough budget year, yet we were supported and had a clear set of choices to make. The process isn't as open as it might be. We hope to decentralize the budget even further, so people can manage their salaries and operating dollars for their own needs."

> "There are dreams emerging here that are not fantastic anymore."
> —Roger Williams, M.D.

Communications and the technology to support improved internal and external communications are the focus of the fourth goal. "When we thought about what we do in CDER, we found we manage information," Woodcock said. "Most of our processes involve information management. The overarching need is to deliver our information to the American public by getting them the information they need about drugs." She cited initiatives to improve communications with CDER employees and with the Center's public constituents, the movement toward electronic filing from industry and the need for improved tracking systems. Woodcock urged Center employees to take advantage of communication opportunities offered to them that would allow them to reach out to CDER constituency groups.

Following the Woodcock's opening remarks, each of the Center's coordinating committees made a brief presentation on how they are facilitating the transformation process within CDER and reaching out to industry, trade associations and other regulatory bodies in this country and abroad. Implementing consistency emerged as a key theme in working to improve the drug regulatory process. "There are dreams emerging here that are not fantastic anymore," remarked **Roger Williams, M.D.,** Deputy Center Director for Pharmaceutical Science. "There could emerge a worldwide set of documents for the drug approval process that would be accepted by all competent national authorities."

Office of Management

Director **Russell Abbott** reported on the Office of Management's plans to provide better database information for chemists and pharmacologists and interface the two databases as well as to improve tracking of Phase IV studies. Abbott reported that CDER would be the first to plant the FDA flag at White Oak if the Center can be consolidated and if the money is appropriated for the move.

Office of Training and Communications

OTCOM Director **Lucy Rose** highlighted the on-going implementation of CDER's World Wide Web site, the continuing analysis of the organizational assessment, and other efforts to enhance training and facilitate the transformation to a fully functional matrix organization. OTCOM's work in progress includes a CDER fact book, an annual report to industry and interactive meetings with constituents, especially through the Center's new videoconferencing capability.

Office of Pharmaceutical Sciences

"One of the great things that has happened is that we have created structures to reach out in a coherent way," said OPS Director Williams. Outreach was exemplified by a report from **Yana R. Mille** on increased coordination between CDER and the U.S. Pharmacopoeia. "The FDA is benefiting because we are learning about off-label uses," she said. "USP is benefiting because they get the perspective of a regulatory reviewer." **Douglas Sporn,** Director of the Office of Generic Drugs, pinpointed efforts at reducing the number of major review cycles by directly contacting the industry and working closely with the three major trade associations. **Weston Metz** highlighted how efforts at the Office of Clinical Pharmacology and Biopharmaceutics to implement the matrix are beginning to break down communications barriers.

Office of Compliance

A series of reports targeted OC's work at prioritizing compliance activities according to health significance and assuring that companies are meeting their manufacturing commitments to supply quality drug products.

Office of Review Management

"Superlatives do not define CDER's performance," boasted ORM Director **Murray Lumpkin, M.D.** He praised the Centerwide achievement in exceeding review time goals established by the Prescription Drug User Fee Act. "We are literally two years ahead of what was expected." Lumpkin reported preliminary data that shows the Center is close to closing out the applications it received in 1994 and 1995. Pending policy issues include a standardized labeling format, post-marketing surveillance, and computer-assisted safety reviews.

Videotapes of the Fall Planning meeting will be available shortly in the Medical Library.