news along the pike

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CENTER FOR DRUG EVALUATION AND RESEARCH

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INSIDE . . .

CDER'S CORNERS

FDA Forum Focuses on Biotechnology Issues

Support for Science-Based Decision-Making Remains High

BY CELESTE BOVÉ

Adjusting to biotechnological advances remains a top priority at CDER, said Center Director **Janet Woodcock, M.D.,** at the FDA Science Forum, held Dec. 8 and 9 the Washington Convention Center.

The meeting was a huge success with 1,114 registrants from FDA, industry, academia and the public. The forum, co-sponsored by the American Association of Pharmaceutical Scientists and the FDA chapter of Sigma Xi, focused on the theme "Biotechnology—Advances, Applications and Regulatory Challenges." **James MacGregor, Ph.D.,** Director of the Center's Office of Testing and Research chaired the two-day meeting.

Leading speakers were:

- FDA Commissioner **Jane Henney, M.D.,** who discussed her priorities for the Agency.
- Dr. MacGregor, who outlined how biotechnology holds the promise of improving safety testing
- David Korn, M.D., of the Association of American Medical Colleges, and Sidney Wolfe, M.D., who both warned about the erosion of FDA's science base.

The lectures and focused discussion groups covered topics such as bioengineered products, microbial pathogens, antibiotics and resistance, novel therapeutic and preventive approaches, diagnostics and detection methodologies, and safety and efficacy assessment. Speakers also addressed regulatory issues related to standards, product quality and the impact of the FDA Modernization Act.

A poster session sponsored by Sigma Xi featured presentations encompassing all areas of FDA regulatory science. Abstracts of the posters and some of the speeches are available

(Continued on page 10)

Henney: Modernization Act, Science Are Top Priorities

Implementing the FDA Modernization Act and enhancing the Agency's science base were the top two priorities identified by the newly sworn-in Commissioner of Food and Drugs in a speech to the Food and Drug Law Institute's annual meeting in Washington Dec. 16. **Jane E. Henney, M.D.,** said her next three priorities would be to focus her attention on the Administration's initiatives for food safety, the safety of the nation's blood supply and tobacco.

"It is very clear that I return to an Agency that is familiar to me but vastly different than the one I left more than four and a half years ago," said Henney, who served as Deputy Commissioner for Operations from 1992 to 1994

"Some things have not changed," she continued. "The FDA is filled with energetic, hard-working, talented people. There are strong traditions throughout the Agency of protecting and promoting the public health. These traditions need to be preserved, and I intend to respect these values."

The Agency has made remarkable progress on the full and effective implementation of the FDA Modernization Act, she said. "Required regulations have been written, guidelines have been published, reports compiled and deadlines met. Remarkably, this has been done without additional resources, and all at a time when the Agency must still attend to its day-to-day business."

She said she is committed to seeing that the Agency's scientific expertise matches the complexity of the new products moving toward the market. "We must apply scientific principles to our product reviews," Henney said.

"We need to be at the top of our scientific game. Thus, we will need to pay particular attention to improving our recruitment and retention of personnel and leveraging the intellectual power of other science-based governmental agencies and academia."

Her comments on food safety, blood safety and tobacco can be found in the copy of her remarks on the FDA Web site at http://www.fda.gov/oc/jhenney.html.

JOE'S NOTEBOOK

"Plain Language: It's the Write Idea!"

That winning entry in FDA's Plain Language Slogan Contest comes courtesy of CDRH's **Stuart Portnoy.** CDER did well with six finalists in the contest, strong evidence of an interest and commitment to the concept. Here are their clever slogans:

- **Mary Kremzner:** "Information that is easy to swallow and good for you, too." and "Plain language, better communication."
- **Frederick Hyman:** "Plain language. Plain simple. Plain smart."
- **Gerald Rachanow** and **Marcia Meyer** (CDRH): "Say it simply."
- **Elsbeth Chikhale:** "Triple S for government language: simple, short and straightforward!"
- **Frederick Hyman:** "Use plain language. It's just plain smart."
- **Joe Hanig:** "When language is plain, there's no need to explain."

You'll notice none of the slogans mentioned how difficult it is to write in plain language so someone else understands you. Seeing and understanding from another person's point of view can take a lot of mental gear shifting.

"When you're a health care professional and use medical language every day, you begin to think everyone understands it," says **Brenda Kiliany, R.Ph.** Brenda and her colleague **Mary Kremzner, Pharm.D.,** write the popular consumer information sheets about new molecular entities that appear on our Web site (page 8). Both are pharmacists and work in OTCOM's Division of Communications Management. Many of you know them already, because they had to consult with you on their project.

Half the story of how that became such a successful Web site so shortly after launch was careful planning, described by **Carol Assouad** in the August *Pike.* The other half of the story is plain language.

There's lots of good advice about clear writing on the government's plain language Web site at http://www.plainlanguage.gov. However, there's a rule of thumb in plain language writing that's been hanging around since the 1950s. It says that to make your writing easy to read, it should have a grade school reading level one whole school level below the educational level of your audience. It's not seeing from that other point of view, but it helps.

If your audience has college degrees, for example, your writing should be high-school level. If your audience is American adults, you can figure most have graduated from high school. To make it easy for most adults to read your writing, it should be at the 7th or 8th grade level. Getting there requires sentences of 25 words or less and only a smattering of big words.

"At first it was very difficult to write at the 8th grade reading level," Brenda recalled. It takes her about two days to write a short patient information sheet based on the labeling, and she's been doing for it six months.

I used to calculate reading levels by hand—a challenge for my mathematically disinclined brain. Now that we all have Word on our computers, it's as easy as running the spelling and grammar checker. If you do that rather than just correct the words with squiggly red underlines, you'll get a useful report on your writing. At the end are two reading indexes. The last one is the grade level score. Both indexes are calculated on the number of words per sentence and the number of big words. This column is at the 8th grade level.

Correction: **Therese Cvetkovich, M.D.,** in the Division of Anti-Viral Drug Products, says that there's potential for confusion in the description of the hypersensitivity reaction to the anti-HIV drug abacavir described in last month's Drugs in the News column (December *Pike).* The hypersensitivity reactions have been described in at least 5 percent of subjects taking abacavir. Though the symptoms usually resolve when the drug is discontinued, there have been fatalities associated with these reactions.

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

Assisting Patients, Families with Trials, Investigational New Drugs

BY JIM MORRISON

Imagine yourself in a doctor's office. You have just learned that your cancer, which was diagnosed two months ago, is not responding to aggressive radiation and chemotherapy. Your doctor is telling you to get your affairs in order because there is nothing more to be done for you. But you aren't willing to lay down and die without having pursued every possible treatment, no matter how tenuous it is. But where do you go from here?

Unless you are at a teaching hospital, your physician may not know of clinical trials being conducted within commuting distance. Even well-informed, educated patients report that finding out about ongoing trials is a singularly frustrating task.

Many patients or their families look to the FDA for assistance. The disease may vary. It may be Alzheimer's, AIDS or the fatal neurodegenerative disease ALS rather than cancer. Because FDA, and more specifically CDER, regulates drugs and drug trials, they expect us to know what is happening and to guide them to the right study.

On the other side of the coin, if you are in CDER and are asked to aid such a patient, you are faced with the constraints imposed by the Freedom of Information Act. This law prohibits us from even acknowledging the existence of an investigational drug unless it has been made public by the sponsor. Often it's difficult to determine whether information about the study has been made public.

That limitation might lead you to think that there is little we can do to aid those who want information about clinical trials of drugs for specific diseases. However, things are changing rapidly.

The FDA Modernization Act of 1997 mandated that the FDA and the NIH work cooperatively to establish and maintain a comprehensive data bank of information on clinical trials for drugs for serious or life-threatening diseases. That data bank has been started. Even without this requirement, there has been a growing trend toward more disclosure of ongoing clinical trials.

The Internet provides a wealth of information about clinical trials that are open to enrollment:

- In the oncology field, the National Cancer Institute lists about 1,600 trials in its PDQ site (http://cancernet.nci.nih.gov/pdq.htm).
- Trials for other diseases are listed in NIH's Web site (http://www.nih.gov/health/trials).
- For more information, NIH lists telephone numbers for a wide variety of organizations that can help patients find needed resources (http://www.nih.gov/news/infoline.htm).
- There is also a for-profit organization that maintains a site with information about trials and protocols (http://www.centerwatch.com).

The second most frequently asked question we get is from patients who are ineligible for a trial but who want to get access to the investigational drug for treatment purposes. Sometimes even patients who have been in a study become no longer eligible to continue because of protocol criteria or because the trial is ending. Yet, if they feel the drug has helped them, they want to continue on it. These patients look to FDA to intervene with the sponsor to allow them to continue to receive the drug.

When we are contacted by a patient, it is only natural to want to assist in any way we can. Certainly, many in CDER do just that very effectively. However, there are limits to the time we can devote to such assistance and to our mandate when interceding on a patient's behalf with a regulated company.

As I mentioned in my last column (December *Pike*), there is a group in FDA whose primary function is to assist patients with serious and life-threatening illnesses. That group is the Office of Special Health Issues. I strongly encourage you to refer patients with cancer, Alzheimer's, AIDS and other such serious diseases and their advocates to OSHI. Unlike CDER staff, they are in a position to contact drug companies on behalf of patients from an advocacy as opposed to a regulatory standpoint. They can be reached at (301) 827-4460.

Jim Morrison is the Center Ombudsman.

Program Gives Cancer Patients Insider's Look at Drug Review Process

Center, FDA Training Partnership Opened Doors and Eyes for 4 Fellows in 1998

A partnership between the Division of Oncology Drug Products and FDA's Office of Special Health Issues arranges for cancer survivors to spend time as temporary government employees at the Center.

The Oncology Patient Fellowship Program provides cancer survivors with a unique educational opportunity to expand their knowledge of the new drug and investigational new drug review process. In a successful pilot conducted last year, four candidates were selected from recommendations made by the cancer community and completed the program.

The fellows first attended the New Reviewer's Workshop followed by training in the DODP. The patient fellows became immersed in the daily working environment of the division—reviewing submissions and action packages as well as attending meetings. They also attended at least two of the division's quarterly advisory committee meetings.

During this process, they developed a keen appreciation for the complexity of the review process, the demands that it places on the review team and the dynamics of the regulatory process involved between industry and the division.

OSHI's **JoAnn Minor** said that the four advocates trained last year arrived with a healthy skepticism about FDA and the drug review process. After completing the training, each advocate left with a sense of confidence about FDA and the work the Agency does.

Leslie Vaccari, DODP's special assis-

(Continued on page 4)

EEO CORNER

February Launches Month-Long Observance of Black History

BY GLORIA MARQUEZ SUNDARESAN

Black History observance begins next month. This offers all of us an opportunity to reflect on and celebrate the contributions of African Americans to the greatness of this country. They come from all walks of life:

- Sons and daughters of slaves transcended difficult lives, educated themselves and became assets to this nation.
- Black athletes have constantly brought honor to this country during Olympic and other sport competitions around the world.
- Others have left their indelible marks in the sciences and the arts.
- African Americans have demonstrated courage in defending the freedom and security of this nation both in times of war and in times of peace.

For these reasons and many more, they deserve our gratitude and recognition.

The whole month of February will be marked with various activities to honor those who made positive impact in the lives of all Americans. Harriet Tubman, Frederick Douglas, Jessie Owen, Jackie Robinson, Marian Anderson, Barbara Jordan and Martin Luther King are some famous heroes. However, among us are also regular everyday heroes: mothers and fathers, firemen and teachers.

These are ordinary people in communities around the country who are selflessly performing their tasks and hardly recognized for their dedication and great service to society. And most importantly, let's not forget our co-workers right here in CDER, nearly 200 tireless African Americans who contribute to the mission and vision of this Center.

In celebration of Black History Month, we plan to have a program with speakers, spiritual songs and poetry reading. **Dorothy Menelas,** the new EEO black representative will organize and conduct this event. Before Dorothy became an official EEO representative, she had volunteered in several special emphasis information sharing and training programs for the handicapped and Hispanics. Last year she was also an active participant in the planning of Diversity Day celebration.

Dorothy, who is originally from Haiti, is multitalented. In all these events, she either sang, narrated or recited a French poem to the delight of the audience. Before joining FDA three years ago, she was an employee at a temporary agency. Dorothy graduated in 1994 from Columbia Union College with a bachelor's degree in English. She was working in the Office of Testing and Research until recently when she moved to the Division of Reproductive and Urologic Drug Products where she received a promotion.

Her goal is to get her master's degree and "work in an area that deals with children, women and minorities." It's no wonder that Dorothy does her EEO volunteer work with great love and enthusiasm. For the great service that she does for the CDER employees, Black History Month is an opportune time for the CDER EEO staff to say, "Thank you, Dorothy."

Gloria Marquez Sundaresan is a CDER EEO Specialist

Office of Compliance Trains Center on Good Manufacturing Practices

BY C. RUSS RUTLEDGE

CDER's Division of Manufacturing and Product Quality is responsible for ensuring that pharmaceutical manufacturers produce drugs for human use in compliance with Current Good Manufacturing Practice regulations, called the CGMPs. This important area of drug quality needs to be assessed before a manufacturer receives approval for an application and in order for a firm to distribute drug products.

Naturally, the CGMPs need to be applied consistently, regardless of the manufacturer's relative size. To ensure that a broad base of CDER staffers have an understanding of CGMP requirements and can use this knowledge as an aid in reviewing applications and support compliance efforts, DMPQ recently presented two "Introduction to CGMPs" courses to Center employees.

In November, this concentrated two-day course was given to approximately 30 CDER project managers. In December, the course was repeated for approximately 36 project managers in the Office of Generic Drugs.

This intracenter communications effort helps establish better interaction between reviewers and the Office of Compliance, resulting in a more uniform application of the requirements.

From OC, the following presenters and their topics were:

- **Paul Motise**—Introduction to the law and regulation; adulteration as it applies to CGMPs.
- **Nick Buhay**—CGMP regulations and current issues.
- **Pat Alcock**—enforcement of CGMPs, compliance programs and work plans.
- **Brian Hasselbalch**—performing a CGMP inspection.
- **Michael Verdi**—regulatory and court remedies to violations of CGMPs.

If your organizational unit has a need for CGMP training, you may contact **Nicholas Buhay,** 4-0093.

C. Russ Rutledge is a compliance officer in OC's Division of Manufacturing & Product Quality.

Cancer Survivors Train on Drug Review Process

(Continued from page 3)

tant and coordinator for the program, works closely with JoAnn to develop training that is individualized to the background and educational needs of each fellow. "We learn certainly as much from the fellows during their time in the division as we impart to them," Leslie said. "They come to us with a refreshing objectivity about cancer and its treatment that we strive not to change. Our goal is to expand their knowledge so that they can go back to their communities and share what they have learned."

For more information about this year's program, contact JoAnn at (301) 827-4460 or e-mail oshi@oc.fda.gov.

—Joe Oliver

Kieffer Takes Reins; Henney Discusses Good Reviewer Traits

BY MELISSA MAUST AND RUSS RUTLEDGE

The Reviewer Affairs Committee is proud to introduce **Lydia Kieffer** as its 1999 chairperson. Continuing her administrative assistant and project manager duties into the new year is **Tanya Abbott.** The committee would like to thank the outgoing officers and division representatives for their time and efforts. Departing 1998 RAC officers are **Melissa Maust,** chairperson, and **Frederick Marsik,** vice chair.

The annual networking event, open to all CDER staff, was held Jan. 25 at the Parklawn Building. Many of you took the opportunity to meet committee members, learn about our activities and discover our plans for the upcoming year.

FDA Commissioner, **Jane E. Henney, M.D.,** our guest speaker, commented on the three qualities of a good reviewer—talent, tone, and tenacity. She reaffirmed her commitment to keeping the FDA a strong science-based organization and discussed how regulatory science research is based in real-world problems compared to the sometimes "romantic" research conducted by academia and the NIH.

Good reviewers, Henney said, have talent—expertise and technical knowledge. They bring the proper tone and a respect for the opinions of others to their dealings with colleagues and industry. Finally, they have the tenacity to get the work done.

Message from departing chair, Melissa Maust:

It was a great year working with primary reviewers in CDER and with CDER's management to communicate the needs and concerns of the primary reviewers. The year was full of highlights for the committee, but there are still a lot of hot issues that will be pursued throughout 1999.

To recap some of the highlights in 1998, we need to begin back in January with the RAC providing support and comments to the start of the CDER Reviewer Career Path pilot program. This is an ongoing program, and the RAC has developed a task force that will continue to work with **Nancy Smith, Ph.D.,** on these efforts. The RAC also participated in the New Reviewer's Workshop held in January.

In February, the RAC was busy preparing for the events that would involve the Team Model Approach to Review of Submissions, the implementation of a Quality of Worklife Subcommittee and final changes to the *CDER Reviewer's Handbook.* The handbook was sent to **Janet Woodcock, M.D.,** for approval.

In March, **Murray Lumpkin, M.D.,** addressed the committee with a detailed discussion of the FDA Modernization Act and PDUFA II. The major issues of discussion were the timing and implementation dates for the Act, the communication of these dates and health economic issues. Dr. Woodcock approved the *CDER Reviewer's Handbook*, and copies were distributed to all of CDER's primary reviewers and will be handed out as part of the RAC presentation at future New Reviewers' Workshops.

In April, the committee was busy updating its by-laws, analyzing the reviewer survey responses, making changes to the *Reviewer's Handbook,* providing comments for the Team Model for **Jean Yager,** as well as discussing issues related to the union and the Quality of Worklife subcommittee. All this was in preparation for the first quarterly meeting, held with the Senior Management Team on May 1.

The agenda for that SMT meeting was full, with the successful result that Dr. Woodcock signed a new set of RAC by-laws. In addition, Dr. Woodcock agreed to have a statement noting her concurrence added to the cover page of the *Reviewer's Handbook.*

On May 20, the RAC presented a memo to Ms. Yager offering comments on the "Proposal for the Enhancement of Multidisciplinary Team Approach to Review of Submissions." RAC again participated in a New Reviewer's Workshop, held in May.

RAC regularly invites guest speakers to our meetings. In June we had two: **Robert Young,** interim chapter president for the FDA union, and **Russell Abbott,** Director of the Office of Management. Dr. Young gave an overview of the NTEU as it relates to the activities and status of the RAC. To this date, there have been no changes in the operations of the RAC.

In July, **Charlene Cherry,** Director, Special Projects Staff, gave an overview of the Government Performance and Results Act and its requirements.

The second quarterly meeting with the SMT was held on Aug. 20. The SMT was briefed on the current status of the Quality of Worklife subcommittee, union issues, team model efforts and comparable pay interests. This meeting was particularly effective and resulted in contacts and support for the RAC.

In September, the RAC briefed the office directors at the Office of Pharmaceutical Science staff meeting. The office directors were interested in continued communications with the RAC. At the request of the Office Directors, the RAC will forward its meeting minutes to them to help improve communication.

In October, the committee briefed the Office of Review Management on its activities and took part in a third New Reviewer's Workshop.

Dr. Smith was our guest speaker for the November RAC meeting, providing an update on the CDER Reviewers Career Path. She summarized the process and gave suggestions on how applicants may improve their packages. This discussion was very informative, and Nancy answered many questions that reviewers had been asking. The Networking Subcommittee announced the date, time and place for the networking event to be held in January 1999, with full support from the Senior Management Team.

And finally, in December, the RAC said goodbye to members with expiring terms and welcomed a new chair and new RAC members. The last quarterly meeting was held and the subcommittee provided a summary of the year's event and an outlook for the new year.

Melissa Maust, outgoing chair of RAC, is a chemist in the Office of Generic Drugs. Russ Rutledge is a compliance officer in the Office of Compliance.

Virus Protection Enhancement; Deadline Met for Desktop Upgrades

BY JUDY MCINTYRE

Updates on Office of Information Technology projects continue. Comments or questions about any of these projects can be e-mailed to the OIT point of contact at the end of each update.

McAfee Virus Protection Software Upgrade: OIT will be upgrading the McAfee VirusScan software to version 4.02 in the near future. This upgrade will secure our computing environment from the latest computer viruses, including the "Microsoft Word Macro 97 Class Virus" currently affecting the CDER environment. This software virus, spread by e-mail, infects Microsoft Word files and potentially can crash networks. You can help protect the CDER computing environment from this and future viruses by being careful to avoid opening documents from sources you don't know. This includes but is not limited to e-mail attachments and diskettes. As a precaution, all diskettes received from an outside source, known or unknown, should be scanned for viruses before use.

The upgraded version of McAfee will be loaded on computers when you log onto the network. The load process may take as long as 10 minutes. As the upgrade is being installed, your computer will reboot several times. Please allow this automated upgrade to complete uninterrupted. If you experience any problem during this upgrade, please report it immediately to the Help Desk at 7-0911.

—**Janice Ausby** (AUSBYJ)

Microsoft Office 97 Implementation in CDER: OIT is pleased to announce that thanks to the planning and hard work of **Hartsell Whitacre Jr., Wil Brooks** and the entire desktop team, the Dec. 31 deadline for Centerwide implementation was met with minimal interruption to our CDER customers.

—Janice Ausby (AUSBYJ)

Year 2000 Activities: Work continues on the 16 CDER mission-critical systems. Testing has been completed on three of these systems. A new server has been configured that will be dedicated to Year 2000 work. The independent verification and validation testing is scheduled to completed by Jan. 31. Preliminary planning has begun to make the year 2000 server available for testing locally developed applications. CDER offices will be contacted to participate. Work continues on infrastructure components such as PCs, servers and telecommunications systems to ensure year 2000 compatibility. Upgrades are being scheduled as required. More information about CDER and FDA's year 2000 activities can be found on the Web at http://www.fda.gov.

—**Judy McIntyre** (MCINTYREJU)

Corporate Database Redesign: During December, the redesign development team held two requirements workshops. The team continued to interview users and attend meetings that have a direct impact on the requirements phase of the project.

Additional workshops will be held starting in February and continuing through the spring. The team is reevaluating the initial plan to complete the design in May. Resources originally assigned to the redesign project were diverted during December and January to work on testing of the mission-critical systems for year 2000.

—**Mark Gray** (GRAYM)

Secure E-mail: The secure electronic mail project, described in the October *Pike*, is been progressing on schedule. A test environment includes two Windows NT servers, several desktop computers and software to simulate several different electronic mail systems, including All-in-One/TeamLinks, Microsoft Exchange and Netscape Internet Mail. The test lab is being used to measure performance of the encryption server under various conditions.

Two pharmaceutical companies with active NDAs have agreed to participate in a pilot starting next month, and a project team is working with several review divisions to enlist CDER participants. After an initial evaluation, additional companies may be added to the pilot. A final evaluation of the secure e-mail system is planned in April. Project documents, including the requirements and pilot design, are available on CDERnet (http://oitweb/oit/) under OIT Activities.

—**Greg Brolund** (BROLUND)

QA Development Project Update: The QA Development Project is currently working on documenting a formal improvement plan. This formal project plan will serve as a roadmap for moving to Capability Maturity Model Level 2. The CMM Maturity Assessment performed in November found nine areas that needed improvement.

On Dec. 2, the project team worked with OIT managers to determine the relative priority for addressing each of these assessment findings in the Improvement Plan. On Dec. 22, the project team presented OIT with an overview of the improvement approach including purpose, scope, objectives, roles and responsibilities, project products and activities, method for managing the project and methods for ensuring quality and configuration management.

Further discussions are needed regarding the scope of the improvement, as well as how CDER priority projects will be managed within the existing organizational matrix. Decisions will be made by the end of January, and the results will be incorporated into the improvement plan.

Information on the QA Development Project is available on CDERnet (http://oitweb/oit/) under OIT Activities. The improvement plan will be posted on CDERnet when it is finalized.

—**Vali Tschirgi** (TSCHIRGIV)

Training Courses: February's calendar for OIT training on MS Office Pro 97 and other programs appears on the next page. The course catalog and the Spring training schedule for all training courses can be found on CDERnet (http://oitweb/oit) under the red training tab.

—**Lana Kostecka** (KOSTECKAL)

Judy McIntyre is a supervisory computer specialist on OIT's QA Staff.

Redesign of CDER's Internet Site Needs Your Help, Input, Ideas

BY CAROL ASSOUAD

The CDER Internet Web site has grown rapidly over its first two and a half years, both in use and content. We have gone from about 10,000 hits in July 1996 to nearly 3 million in November (compared to 12 million hits for the entire FDA site). From several hundred visitors a month, we now have nearly 200,000 a month (nearly 800,000 total FDA). During that time, we've had to upgrade the FDA Internet server four times to accommodate the growth and increasing number of interactive databases on it, such as CDER's *Orange Book.*

But the content, too, has grown both in quantity and in presentation sophistication, ranging from simple to complex documents in HTML, PDF and text, and incorporating frames-based pages, graphics, Powerpoint presentations, form templates and interactive databases.

Our very simple site structure has been stretched to accommodate this growth in content and complexity. Currently, it is composed of four organizational categories—About CDER, Regulatory Guidance, Drug Information and What's Happening. These are supplemented by four navigational aid buttons—FDA Page, Search, Comment and What's New. You only need to look at the New Drug Approval Information table to see that we urgently need to restructure the site so that finding information is more intuitive and, once located, is easier to use and more comprehensible.

I can't possibly exaggerate about how much all of us on the Web Resources Team have learned on this project—not just about the technology, but about leadership, coordination, knowledge management and, most importantly, listening to our customers. So I'm back, once again, asking for your help and input on a proposed redesign of the site.

This proposal is based on our experience, a review of other government and commercial Web sites and the comments of our users to date. We want to rapidly widen the circle of comments on the proposed redesign, starting with you, moving to Agency staff and then out to external users and focus groups.

I'd like to have very open dialogue about the proposal, so I urge you to use the discussion forums set up on CDERnet's Information Management Page at http://cdernet/infomgmt/informgmt-frames.htm.

Please comment on any or all of the following issues and categories. Please remember Web site principle No. 1: Information is not duplicated on the site but it may be linked to or from more than one category.

Front or Home Page: Do we want to retain the current page design that contains only the information categories? Or do we want to take the more popular approach and have an entrance page that contains news about CDER initiatives and major drug approvals?

Six Major Information Categories:

About CDER—Similar to what's currently there: mission and vision, people, organizational structure, lead-ins to office and division pages and to committees and task forces.

Drug Information—Users want all kinds of drug information, including approvals, reviews, identification of drugs and adverse effects. This area would be vastly expanded and would include a drug information and identification database.

Regulatory Information—Similar to the existing category but multilayered so users don't need to page through several opening screens of alphabetical listings.

Special User Groups—Here would be materials developed for specific user groups, such as consumers, patients, the elderly, children, non-English speaking persons and international audiences.

CDER Archival Information/FOI Reading Room—This would hold superseded guidances, drafts of now-completed guidances that were posted for public comment, older drug information, such as reviews older than a to-be-determined date. We need to establish time frames or hit rates for category-specific information so we can methodically remove old material.

What's Happening—Calendar information; meetings, conferences and workshops, including associated agendas, presentations and handouts, abstracts, transcripts and minutes; new CDER publications; task force schedules; and status reports on guidance documents.

Five Navigational Categories:

To Agency-level page.

Search.

Comments—Includes the triage now used for Web questions vs. drug questions, but with links on how to contact us for specific information, the CDER Quick Index approach.

Site Information—Site structure, copyright permissions, statistical information, site scope and focus.

What's New—Lists all material posted to the site during the past 30 days.

Please take some time to look at the proposed outline and let us know what you think about this and identify any major problems with it, such as information gaps or potential access/usage problems.

Carol Assouad is Division Director, Medical Library, and Program Manager, CDER Web Sites.

February OIT Training Calendar

Monday	Tuesday	Wednesday	Thursday	Friday
1 **Acrobat Intro** 9-11:30 **LAN** 1-3:30	2 **Word Intro 1-3:30**	3 **Word Formatting** 9-11:30 **Word Tables** 1-3:30	4	5
8	9	10	11	12
15	16 **PowerPoint Intro** 1-3:30	17 **Word Intro** 9-11:30 **Word Formatting** 1-3:30	18 **Word Tables** 1-3:30	19 **Access Intro & Tables** 9-11:30 **Access Queries & Reports** 1-3:30
22	23	24 **NEST** 9-12 **NEDAT** 1-4	25 **DFS** 1-4	26 **NEDAT** 9-12 **MS Project for CDER Project Managers** 1-4

Ajaz Hussain to Head Division of Product Quality Research

The Office of Testing and Research is proud to announce the selection of **Ajaz Hussain, Ph.D.**, as Director, Division of Product Quality Research (DPQR). Dr. Hussain joined the Center in January 1995 in the old Division of Biopharmaceutics to promote research in support of regulatory review.

When the Office of Pharmaceutical Science was established in October 1995, Dr. Hussain was assigned to the Product Quality Research Staff (formally the Formulations Staff) to focus on directed research that supports and enhances the science base of product quality review through guidance development and regulatory policy. This staff was absorbed into the DPQR in 1996.

Dr. Hussain has served as DPQR's deputy and has been the acting division director since August. He came to FDA with an exceptional background in pharmaceutics and biopharmaceutics having received his Ph.D. in biopharmaceutics from the University of Cincinnati. While at Cincinnati, he received the Merrell Dow Research Scholarship which allowed him to acquire industrial research experience at the Merrell Dow Research Institute for two years investigating a variety of manufacturing problems.

After receiving his Ph.D., Dr. Hussain served as an assistant professor of pharmacy at Ohio Northern University and an associate professor of pharmaceutics at the University of Cincinnati. He served as a consultant to a number of pharmaceutical companies to provide expert advice on formulation issues.

Dr. Hussain's broad expertise has been invaluable to OPS in developing and implementing a number of significant guidances. As chair of CDER's Biopharmaceutics Coordinating Committee's expert working group, he has spearheaded the development of the a Biopharmaceutics Classification System guidance document.

He serves on a number of expert working groups in the Center including chairing the working group to revise SUPAC-IR. Dr. Hussain is often called upon to perform expert reviews of submitted data, particularly in aspects relating to the effect of excipient changes and their possible impact on product performance and to address other issues of biopharmaceutics in reviews, especially in the area of dissolution test methods, *in vitro* to *in vivo* correlations and transdermal drug delivery systems.

He is an expert in artificial neural networks and computer expert systems, especially their application to pharmaceutical problems. Dr. Hussain has played a critical role in the development and implementation of a CDER initiative to collaborate on enhancing research capabilities to generate data to support policy directed at product quality aspects of regulatory filing. This initiative has lead to the American Association of Pharmaceutical Scientists' partnering with industry and academia, to create the Product Quality Research Institute.

Through PQRI, FDA hopes to collaborate with industry and academia on research and training to support future regulatory policy and guidances. Under Dr. Hussain's direction, the DPQR will play an important role in ensuring a strong science base to meet the regulatory challenges of the 21st century. DPQR will maintain a number of research programs which will provide a base for supporting regulatory and policy decisions essential to meeting CDER's mission.

Feb 1 Deadline Looms for Spring Course Registration with DTD

By Amy Mason

The Division of Training and Development is pleased to announce the 1999 spring semester. Registration for spring courses is now underway and will continue through Feb. 1.

Similar to semesters in the past, DTD's spring 1999 course schedule is available on CDERnet. Links to the spring schedule can be found on CDERnet in two places: http://cdernet/dtd/catalog.htm and http://cdernet/dtd/what/courses/course.htm.

Registration instructions and the TeamLinks electronic registration form can be found on these links. Management officers have been furnished with a paper copy of the schedule for reference if needed.

DTD has added two new programs to their already extensive offerings this semester. The new programs are Interpersonal Communication and Facilitation Services. Information regarding the courses under the two new programs as well as our other programs can be found under their respective links on CDERnet.

The other offerings are grouped under Orientation Programs, Reviewer Education Program, Advanced Science Education, In-Service Training, Project Manager Certification Program, "New Horizons" CDER Secretarial and Support Staff Career Development Program, Leadership and Management Development, Medical Library, Office of Information and Technology and Distance Learning Satellite Program.

If you would like additional information regarding DTD's Spring Course Schedule, please call the Division of Training and Development at 7-4580.

Amy Mason is an education training assistant in DTD.

Consumer Drug Information Web Site Proves Popular

Since the August introduction of consumer information about new molecular entities, that site has quickly blossomed into one of the most frequently accessed locations on CDER's Web site, receiving about 12,000 hits a month.

The site has easy-to-read, patient friendly summaries for new molecular entities, beginning with those approved last year. Currently, it ranks 14th in popularity, right behind the *Orange Book* and the listings of guidances, approvals and advertising letters.

In OTCOM's Division of Communications Management, **Brenda Killiany, R.Ph.,** and **Mary Kremzner, Pharm.D.,** write the summaries. They coordinate with the review divisions; **Nancy Ostrove, Ph.D.,** and **Ellen Tabak, Ph.D.,** Division of Drug Marketing and Advertising; and CDER's webmaster, **Paul Stauffer,** Medical Library.

FDA OK's First Cox-2 Inhibitor, Treatment for Painful Leg Disorder

FDA has approved the first Cox-2 inhibitor for arthritis and the first treatment in 15 years for the painful leg disorder intermittent claudication.

FDA on Dec. 31 approved celecoxib, a new product to treat rheumatoid arthritis and osteoarthritis. Celecoxib is a non-steroidal anti-inflammatory drug that blocks production of prostaglandins by inhibiting the enzyme cyclooxygenase-2, known as Cox-2.

Unlike other NSAIDS, celecoxib does not inhibit the enzyme cyclooxygenase-1 or Cox-1. Inhibition of Cox-1 is believed to contribute to some of the adverse effects of NSAIDS, including upper gastrointestinal ulcers. It is hoped that celecoxib will have safety advantages compared to other NSAID products. Additional studies and post-marketing experience will add substantially to the understanding of how the overall risks and benefits of celecoxib compare with those of other NSAID products.

Celecoxib was found to be an effective arthritis treatment in placebo and active-controlled clinical trials that enrolled 2,100 patients with rheumatoid arthritis and 4,200 patients with osteoarthritis.

The drug was compared to other NSAID products in several of these clinical trials by using endoscopes to determine the incidence of stomach and upper intestinal ulcerations following the use of these products. These studies showed that patients taking celecoxib had a substantially lower risk of ulcers detected by endoscopy over the study period of 12 to 24 weeks compared to patients who took other NSAIDS.

However, NSAID products can cause a range of gastrointestinal problems, and patients with endoscopic ulcers may often recover without special treatment and without experiencing any serious symptoms or complications. Therefore, additional studies in many thousands of patients would be needed to see whether celecoxib actually causes fewer serious gastrointestinal complications than other NSAID products.

Until such studies are done, the drug labeling for celecoxib will include the standard warning for doctors and their patients about the risks associated with all NSAIDS, including risks of GI ulceration, bleeding and perforation. The labeling advises patients taking these drugs to be alert for ulceration and bleeding that can occur with or without warning. Patients should promptly report signs and symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or swelling to their physicians.

In addition, celecoxib does not affect platelet aggregation, an important part of the blood clotting process. Many other NSAID products can interfere with platelet function, which may increase the risk of bleeding complications in some patients. Celecoxib does not appear to be different from other NSAIDS in its effects on the kidneys.

Celecoxib is marketed under the brand name Celebrex by Searle of Chicago, Ill.

FDA has approved cilostazol, a new drug for treating stable intermittent claudication, a severe pain, aching or cramping in the legs that occurs with walking. Intermittent claudication results from peripheral arteriosclerotic vascular disease—a condition more commonly known as atherosclerosis or hardening of the arteries. The condition results in an inadequate blood supply to the leg muscles. This drug is the first to be approved for this indication in more than 15 years. More information, including the summary of approval and the advisory committee transcript can be found on CDER's Web site at http://www.fda.gov/cder/news/cilostazol/default.htm.

Cilostazol has not been evaluated either for safety or effectiveness among patients with more severe peripheral vascular disease who have claudication pain at rest, leg ulcers or gangrene.

Cilostazol was studied in eight clinical trials (most of three to six months duration) that enrolled patients with intermittent claudication whose ability to walk short distances was severely compromised. In six of the eight studies, patients treated with cilostazol, compared to those treated with placebo, were able to walk farther before claudication began and before the pain became intolerable and forced them to stop walking.

Additionally, patients treated with cilostazol reported a greater increase in both walking distance and walking speed during daily routines.

Clinical studies in several thousand patients did not identify serious toxicity, but two important concerns with the use of cilostazol are identified in labeling for the drug and in a patient-directed brochure.

First, cilostazol is pharmacologically related to a group of drugs studied for heart failure, the phosphodiestrase III inhibitors. Several of these have shown increased death rates in patients with severe heart failure. It is unknown what effect these drugs have on people with less severe heart failure or no heart failure.

Cilostazol was studied in about 2,100 patients with claudication, many of whom had other conditions such as a history of heart attacks or diabetes, but the patients did not have severe heart failure. In the patients studied there was a low mortality rate, 0.8 percent in patients treated with cilostazol, 0.7 percent in placebo patients. There was insufficient evidence to determine whether cilostazol has an adverse survival effect in patients without heart failure. The manufacturer plans to further study the mortality effect in sicker patients with claudication.

The second concern is that cilostazol has not been studied in combination with clopidogril, a drug recently approved for use in patients with peripheral vascular disease to reduce the rate of serious events such as heart attacks, stroke and death. Clopidogril was unavailable while cilostazol was being developed. Concern arises because both cilostazol and clopidogril inhibit platelet function, and it is possible that combined use could lead to excessive bleeding. Cilostazol was, however, used with aspirin, which also inhibits platelet function, without an apparent adverse interaction (increase in bleeding).

The drug will be marketed under the trade name Pletal by Otsuka American Pharmaceutical Inc. of Rockville, Md.

Source: FDA talk papers.

Biotechnology Poses Challenges, Opportunities to Regulators

(Continued from page 1)

on FDA's intranet at http://first.fda.gov/sf98/.

Dr. Woodcock cited diagnostics, synthetics, drug delivery systems and patient-specific therapies as areas that challenge the Center to keep pace with biotechnology advances. She pointed out that the technology for safety testing lags behind that for drug discovery. Advances in toxicology need to keep pace with new technology. In the area of gene therapy, she pointed to the large gap between identifying genes and figuring out how they work.

Clinical testing methods lag behind technology and could create bottlenecks, particularly on safety and efficacy, she said, and need to get away from empirical methods. Pharmacology also needs to be clarified for new products. To help get there, she said FDA needs better collaboration among disciplines and centers as well as improved computer systems.

Dr. Henney opened the forum and emphasized that among her top priorities are implementing the letter and spirit of the FDA Modernization Act and strengthening the Agency's science base.

OTR's Director Dr. MacGregor said the biotechnology revolution has resulted in major advances in our understanding of the molecular biology of cell and tissue functions and has provided an impressive array of new technologies. These advances create major opportunities for improved non-clinical and clinical safety assessment, including:

- Damage-inducible responses as indicators or biomarkers of functional damage to cells and tissues.
- Genetic technology for individual genotyping and monitoring of mutations and genetic polymorphisms.
- Transgenic technologies to build new animal models with engineered characteristics, such as rapid tumor formation, humanized receptors and recoverable genetic targets.
- Improved biomarkers of cell and tissue pathology.

Dr. Korn, who chaired the FDA Science Board committee that reported on the Agency's science base in 1997, commented that FDA has linked its regulatory responsibilities with the conduct of original research. Astonishing and rapid advances are transforming the scientific and technological disciplines. These advances are translated into new classes of medical products with unprecedented rapidity. The need for scientifically astute regulation—informed and supported by an intramural base of mission-focused, high quality, well-organized and well-managed scientific research—has never been more compelling, he said. Dr. Wolfe echoed Dr. Korn's concerns that FDA's science base continue to receive support.

One of the highlights of the second day of the Forum was the presentation of the 1998 FDA Scientific Achievement awards (December *Pike),* including a new award for outstanding intercenter scientific collaboration.

The Forum concluded with a panel discussion among FDA's center directors and other invited speakers who summarized their views about science and technology advances.

Dr. MacGregor was commended for his efforts to include leading speakers from industry and academia in addition to FDA's scientists and regulators, which contributing greatly to the forum's success.

Celeste Bové is a health scientist administrator in OTR.

FDA Warns About Products with GBL, Asks for Voluntary Recall

FDA alerted consumers on Jan. 21 not to purchase or consume products, some of which are labeled as dietary supplements, that contain gamma butyrolactone, abbreviated as GBL. The Agency asked the companies that manufacture these products to voluntarily recall them. FDA has received reports of serious health problems—some potentially life-threatening—associated with the use of these products.

Although labeled as dietary supplements, these products are illegally marketed unapproved new drugs. Products containing GBL are marketed under various brand names including Renewtrient, Revivarant or Revivarant G, Blue Nitro or Blue Nitro Vitality, GH Revitalizer, Gamma G, and Remforce. They are promoted with claims to build muscles, improve physical performance, enhance sex, reduce stress and induce sleep.

GBL is also known by the chemical names 2(3H)-furanone dihydro; butyrolactone; gamma-butyrolactone; 4-butyrolactone; dihydro-2(3H)-furanone; 4-butanolide; 2(3H)-furanone, dihydro; tetrahydro-2-furanone; and butyrolactone gamma.

GBL-related products have been associated with reports of at least 55 adverse health effects, including one death. In 19 of those cases, the consumers became unconscious or comatose. Several required intubation for assisted breathing. Other reported effects included seizures, vomiting, slow breathing and slow heart rate. There are reports of at least five children under 18 years of age who have been injured or who have suffered these kinds of effects.

When taken orally, GBL is converted in the body to gamma hydroxybutyrate or GHB, a very potent unapproved drug. GHB is currently being investigated under the supervision of doctors for the treatment of narcolepsy. Because of its serious side effects, GHB should only be taken in the context of these FDA approved investigations. FDA and the Justice Department have ongoing criminal enforcement actions against GHB. GBL should not be taken.

Products containing GBL are sold in liquid and powder form. They are sold via the Internet, in some health food stores and in some gymnasiums and fitness centers.

Consumers are advised to dispose of any products of this type in their possession. If they have experienced adverse health problems from use of these products, they should promptly contact a physician. FDA requests consumers and physicians to report adverse events to FDA's MedWatch 1-800-332-1088.

FDA is considering all potential regulatory actions at its disposal if products containing GBL are not recalled. The Agency will act expeditiously to protect the public health.

Source: FDA Talk Paper.