news along the pike

Center for Drug Evaluation and Research

April 1998

Volume 4, Issue 4

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Pike's Corners . . .

National Library Week

Research Tools Available Through Browser

By Carol Assouad

CDER's Medical Library has planned a number of activities to celebrate National Library Week, April 19 to 26. To kick off the week, **Kathie McConnel** and **Wendy Cheng** will present a CDER Forum April 21 called, "National Library Week: Hidden Treasures on the Library Homepage."

Other events planned for National Library Week include a "treasure hunt" contest for library users; an open house April 23 from 1 p.m. to 3 p.m. at the main library in Parklawn 11B-40; and open houses at the branch libraries on April 24 in Corporate Boulevard, Room S-121, from 9 a.m. to 11 a.m., and Woodmont II, Room 3001, from 1 p.m. to 3 p.m.

The library was too excited about MLWeb, its CDERnet home page, and WebLERN, the web version of the Library Electronic Reference Network, to wait for National Library Week to introduce them. Both have been up and running on CDER's intranet since the middle of March.

On MLWeb, you can see how the library is

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Parklawn Classic April 24

Registration Closes April 23

By Bronwyn Collier

CDER runners and walkers who want to take part in the 23rd annual Parklawn Classic on Friday, April 24, at 11 a.m. must register by Thursday, April 23.

The event takes place rain or shine and includes a 5-mile run and a 2½-mile walk. Runners who register by April 22 will pay a $10 fee. It will cost $20 to register on April 24. Unlike previous years, there is no race day registration. All runners receive a T-shirt. There is no fee to register for the walk, and walkers can purchase a T-shirt at the Parklawn

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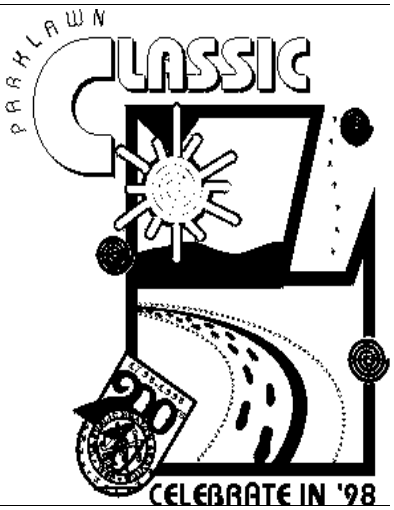

Aims at Reducing Animal Studies

Artificial Intelligence Targets Toxicology

By Joseph F. Contrera, Ph.D., and Edwin J. Matthews, Ph.D.

In last month's *Pike,* we reported on the Office of Testing and Research's cooperative research and development agreement to enhance an artificial intelligence structure activity relationship software product to improve its prediction accuracy. A mission of the Regulatory Research and Analysis Program at OTR is developing toxicology databases and applying information to benefit regulatory review and new drug development.

There is a clear need for rapid, efficient and cost-effective means to screen molecules for potentially adverse toxicological properties before they are tested in animals. Currently, the pharmaceutical industry has efficient automated tools for rapidly screening large numbers of molecules for potential efficacy. Today's high-throughput technology can rapidly evaluate compounds for binding to a specific receptor, for example, and generate thousands of candidate molecules.

The identification of promising "lead" compounds however, also requires an

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Joe's Notebook

A Partnering Case Study

Those of you who attended the April 14 CDER Forum heard **Marsha Henderson** of FDA's Office of Women's Health describe the development of the "Use Medicines Wisely" campaign aimed at under-served women (page 5). The campaign shows how partnering with other organizations magnifies our efforts. Cooperating and collaborating are CDER transformation goals. In Marsha's case, she estimates she was nearly eight times as effective partnering as going alone. When she ran the pilot programs in Hartford, Conn., and Chicago, she anticipated handing out 30,000 pieces of information. With partnering, she actually distributed 235,000.

The CDER Forum series, by the way, takes place Tuesdays (except the first Tuesday of the month) from noon to 12:45 p.m. in Parklawn 13B-37 and is videoconferenced to Woodmont II, Conference Room G, Corporate Boulevard, Room S-100, and Metro Park North I, Room 259.

Upcoming Forum presentations are:

- April 21, **Kathy McConnnell** and **Wendy Cheng,** "National Library Week: Hidden Treasures on the Library Homepage."
- April 28, **Carolann Hooton** and **Carol Assouad,** "Electronic Freedom of Information."
- May 12, **Karen Kapust,** "Introducing WebLERN." (See page 1.)
- May 19, **Janet Woodcock, M.D.,** "Center Director Conversation."

For more information or to schedule a presentation, contact **Laura Bradbard** by e-mail (BRADBARDL) or phone (7-3788). Laura, a fellow OTCOM employee, says the Forum provides an excellent opportunity for you to present information about your programs that is of broad interest to CDER and obtain feedback. You can check out tapes of past CDER Forums from the Medical Library.

Up-to-Date *Quick Index* Available . . .

Another OTCOM colleague, **Crystal Wyand,** reports that the popular *CDER 1998 Quick Index* is now available on the Web. You can access it at: http://www.fda.gov/cder/directories/qi98.pdf. Printed copies are scheduled to be distributed to CDER later this month.

Make the Connection on April 27 . . .

Devota Herbert reminds secretaries and support staff that brunch will be served at their April 27 meeting at the Gaithersburg Hilton. Registration starts at 8:45 a.m. Center Director **Janet Woodcock, M.D.,** will be giving the keynote address. OTCOM's **Debbie McKemey** will conduct an icebreaker. **Tanya Abbot,** from the Executive Operations Staff, will discuss organizing a coordinating committee. Debbie returns with a team-building exercise. **Sarah Thomas,** also from OTCOM, will talk about the "New Horizons" professional development program (March Pike). Finally, emcee Devota will wrap it all up.

Long Exercise for Public Health . . .

There are more ways than just the Parklawn Classic (page 1) to exercise for public health. **Cathie Schumaker,** who, you'll recall from last month's Notebook, is training for the 350-mile four-day AIDS Ride from Raleigh, N.C., to Washington, provides this update: "I bought a hybrid bike and have been able to increase my speed from 10 miles per hour to 12½ miles per hour—which means two hours less on the bike for every 100 miles! I am riding about 80 miles per week and completed a 60-mile ride on April 5." Cathie, who was off to Hilton Head where she hoped to ride every day, said she's surprised that she hasn't heard from anyone else doing the ride. We know you're out there. Send her an e-mail at SCHUMAKER.

news along the pike

The Pike is published electronically on the X:drive in Cdernews and on the World Wide Web at:

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

Photocopies are available in the Medical Library (Parklawn 11B-40) and its branches (Corporate Boulevard S-121, Woodmont I 200-S, and Woodmont II 3001).

Views and opinions expressed are those of the authors and do not necessarily reflect official FDA or CDER policies. All material in the Pike is in the public domain and may be freely copied or printed.

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

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Ombudsman's Corner

When a Drug Isn't a Drug

By Jim Morrison

Responsibility for determining where FDA-regulated products belong rests with the Agency's Ombudsman, **Amanda Norton.** My job as the Center's Ombudsman includes being CDER's point person for intercenter jurisdiction. Before becoming involved with intercenter jurisdiction, I had little idea about the number and variety of products that fall into the gray areas between centers. Besides the 30 to 40 formal requests for designation filed with Amanda Norton's office each year, there are many informal questions from prospective applicants about which center should review their product.

Three intercenter agreements, developed and signed in 1991 by the three centers that review medical products, describe the rules for deciding product jurisdiction. Those documents, each one involving two centers, are helpful, but cannot describe every possible product. Anyone who does this work quickly develops sympathy for the regulatory affairs people in the industry who must decide which center has jurisdiction over their proposed product. Those of us inside the Agency have significant difficulty deciding where some products belong, and we have access to prior decisions about investigational products that cannot be disclosed to those outside the Agency.

We occasionally find products reviewed in CDER that belong elsewhere or are very similar to other products in another center. Correcting the misdesignation is very difficult when the product has already been approved or is far along in the review process. This article is my plea to staff in CDER for help in identifying products that really belong in another center.

Although product sponsors have the first opportunity to make the decision on jurisdiction, they may not be unbiased in their choice. If a product might arguably be a device or a drug, many sponsors prefer device status to avoid user fees and to be subject to what are perceived as less stringent requirements. Thus, sponsors often submit the product for review as a device and look to the Agency to tell them if they are wrong. Conversely, some drug companies would prefer that their products be regulated as drugs to benefit from exclusivity or because they are more comfortable with the CDER review process.

The consequences to the Agency and to sponsors of misdirected applications can be substantial, but they are less severe when the problem is identified early in the product's regulatory life. Whether misdesignation occurs by inconsistent Agency decisions over time or by a failure to recognize an error, the courts look unfavorably on the Agency when virtually identical products are regulated by different centers. A recent court opinion involving the assignment of some ultrasound imaging agents to Center for Devices and Radiological Health and others to CDER stated that assigning similar products to different regulatory jurisdictions is by definition arbitrary and capricious.

Later this year, I hope to distribute to the new drug project managers an algorithm that will help them decide when a product belongs in CDER.

In the meantime, if you see an IND for a product that seems to belong in CDRH or the Center for Biologics Evaluation and Research, or if the product appears to be a combination drug/device or partly composed of a substance that may be CBER's, please discuss it with your supervisor and let me know. Likewise, if you get a consult from another center for a product that you think really belongs in CDER, question it. Your instincts may well be right. Even if you are wrong, you will learn something about product jurisdiction, and you will earn our gratitude for being alert to possible problems.

Jim Morrison is the Center's Ombudsman.

Pediatrics Corner: Draft List of Drugs Needing Pediatric Data Posted

By Kathy Robie-Suh

In an effort to garner information about how marketed drugs may be used with their approved indications to help children, the FDA has compiled a draft list of those drugs which would most benefit from this type of pediatric data.

The FDA list, which requires FDA to consult with experts in pediatric research to develop, prioritize and publish a list of approved drugs "for which additional pediatric information may produce health benefits in the pediatric population."

Drugs on the list had to meet one of the following criteria:

- Represent a significant improvement over marketed products.
- Be widely used in the pediatric population as measured by at least 50,000 prescription mentions per year.
- Be in a class or for a use where additional therapeutic options for children are needed.

Working through the CDER Pediatric Subcommittee, FDA consulted with pediatric experts to develop the draft criteria and draft list of approximately 400 drugs. The review divisions within CDER each assessed appropriateness of drugs reviewed by their division for inclusion on the list.

The draft list may be examined on the CDER Internet site at: http://www.fda.gov/cder/pediatric. Drugs are shown by therapeutic class as defined by the CDER division where the drug was reviewed. Drugs are in alphabetical order within each class by active ingredient with all approved indications for which additional pediatric information may produce health benefits. Uses of the drugs in children for indications unapproved in adults—off-label uses—are excluded. The list is unprioritized. The final, prioritized list will be published on or before May 20, after which the subcommittee will update the list regularly.

Comments or suggestions on prioritizing the list are welcome and should be sent to **Khyati Roberts,** Executive Operations Staff, (ROBERTSK).

Kathy Robie-Suh is a Medical Officer in the Division of Gastro-Intestinal and Coagulation Drug Products and a representative on the CDER Pediatric Subcommittee.

Information Technology Corner

OIT on Track to Fix Millenium Bug in Corporate Programs

By Jim Baughman

What is the year 2000 problem?

A little history may help explain the problem. In the early 1960s, when external storage devices were costly and data entry was labor-intensive, data processing professionals sought efficiencies in storing, entering and displaying data. Date representations were entered and stored as six-digit date fields (mm/dd/yy), accounting for only the month, day and year of the date. The century was implied and not explicitly stored. This is a workable solution until 21st century data are introduced, and then programs lose the ability to distinguish between dates. Thus, in the commonly used mm/dd/yy format, June 19, 1900, is stored precisely the same as June 19, 2000—06/19/00.

In order to be year 2000 compliant, an application must:

- Correctly process dates before, on and after Jan. 1, 2000.
- Recognize year 2000 as a leap year.
- Accept and display dates unambiguously.
- Correctly process logic used for non-date functions, for example, calculating age from a birth date.

What is OIT doing about CDER's corporate applications?

There are three broad approaches to handling the problem: replace, repair or retire. Repairing includes adding custom programming to existing applications, managing patches applied to existing vendor packages and converting existing data to work with enhanced applications.

Two years ago, CDER had 31 mission critical corporate applications and one non-mission critical. On March 25, a reclassification analysis resulted in the one non-mission critical system retaining its status, 12 systems being downgraded to non-mission critical and four systems being retired. This left 14 corporate applications classified mission critical. Regardless of their status, all systems are scheduled to be year 2000 compliant by December 31. However, the mission critical systems will require additional testing by an independent contractor.

OIT submits periodic status reports to FDA's year 2000 coordinator who, in turn, provides consolidated FDA reports to HHS and the Office of Management and Budget.

What about locally developed applications and personal computers?

If you have developed a local application or report that uses the six-digit date format (mm/dd/yy), OIT recommends that you repair the application or report by incorporating an eight-digit date format (mm/dd/yyyy) to make it year 2000 compliant and avoid potential data integrity problems. If you have no plans for repair, you need to replace the application or report with one that will be year 2000 compliant or retire the application or report altogether. It is your responsibility to resolve the problem.

You should note that local applications developed using four-digit years may still have problems. If calculations are done, make certain they handle the fact that the year 2000 is a leap year. All interfaces need to use four-digit years consistently.

If you have CDER-owned 386s or 486/25 PCs in your office or home, please contact your focal point for a replacement. Replacement PCs will be provided when available. If you are only using the home PC for e-mail and nothing else, you will not be affected. The dates attached to e-mail messages are system generated, and the system date is already year 2000 compliant.

We recommend that you check with OIT before performing any year 2000 tests on hardware; otherwise, you risk operational failure and possible loss of important files.

What about commercial-off-the-shelf products?

You should be aware that commercial products, such as the Microsoft Office suite, deal with the year 2000 issue in various ways, even within the same product line. Also, different versions of the same program may treat dates differently.

Need more information?

If you have questions concerning year 2000, please go to the OIT's CDERnet site, choose the Forms button and submit your question using the year 2000 form. CDER's year 2000 coordinator, **Jim Baughman,** will research your question and get back to you as soon as possible. A more comprehensive version of this document can be found on the OIT's site: oitweb/oit.

Jim Baughman is a computer specialist in the Technology Support Services Staff.

Medical Library's CDERnet Site Features Research Tools

(Continued from page 1)

organized in About ML. You can apply for borrowing privileges, request a search or recommend a journal or book for purchase in Request Forms. You can read the Library's newsletter, *Check It Out!,* in Library Publications. In Other Information Resources, you will find hundreds of evaluated Internet sites classified under 36 subject areas. This page is compiled and annotated by librarians, **Karen Kapust** and **Nancy Muir.** Please let them (KAPUSTK or MUIRN) know of new sites to add.

You can get to WebLERN from MLWeb or just type WebLERN in the browser address field. Once you've done this, you're ready to explore some old standbys and some great new products, such as *Goodman and Gilman's Pharmacological Basis of Therapeutics, Harrison's Principles of Internal Medicine* and *Stat!-Ref,* a compilation of 30 full-text medical references. You can also read *The Pink Sheet* before the mail version reaches you. This is a no-cost pilot worked out with the publishers, FDC Reports, by our information resources development team leader, Karen Kapust. Please e-mail Karen (KAPUSTK) or use the Request Form to have us look into additional electronic titles that would be useful to you.

MLWeb is a dynamic page, and the current version is only the beginning. To suggest improvements to the MLWeb, contact Kathie McConnell (MCCONNELLK) or Wendy Cheng (CHENGW).

Carol Assouad is the Medical Library Director.

Strategic Planning Corner

CDER Moves Toward Performance-Based Management

By Charlene Cherry

The Prescription Drug User Fee Act introduced CDER to performance-based management and gave us a good idea of what would be in store for the coming years. Why has government moved towards performance-based management and away from the traditional approach of activities, inputs and outputs? Is performance-based management a better way of doing business?

To answer these questions, you'll first need to understand what performance-based management is. It's a process of setting a strategic direction, defining annual goals and measures and reporting on performance. Traditionally, government agencies have focused on program activities and staffing—what we are doing and how many people it takes to do it. Performance-based management focuses on results—setting goals and measuring our progress toward achieving those goals.

FDA's first annual performance plan was incorporated in the fiscal year 1999 budget justification sent to Congress and the Office of Management and Budget in February. The plan includes performance goals for the human drugs program for fiscal year 1999. The human drugs portion of the plan is available for your viewing on the Office of Management's intranet home page under the Reference section or directly at http://cdernet/om/cderprog.pdf. The FDA Plan, which will be posted to the FDA Web site after OMB review, includes only a few of the goals CDER identified for its 1999 plan. CDER's fiscal year 1999 goals and measures, a compilation of all CDER goals along with strategies, measures, baselines and contact person is also on OM's site at: http://cdernet/om/99Perfplan.pdf.

The FDA performance plan is the result of an hierarchy of performance goals and measures from all the centers. When the Agency plan was assembled, some CDER goals and measures were excluded. This doesn't mean those goals lack importance. If all goals were to be included, it could represent too much data and obscure rather than clarify performance issues.

As an example, let's look more closely at one CDER goal included in the Agency plan: "By the end of FY 1999, CDER will: (a) evaluate the availability, quality and usefulness of prescription drug information provided to individuals receiving new prescriptions; and (b) complete two studies that will aid in development of comprehensive drug information."

What makes this goal significant? First, FDA has been designated as a "high impact agency" by the National Partnership for Reinventing Government, formerly known as the National Performance Review. High impact agencies are those that have the most interaction with the public and business community. The NPR (it keeps the same initials) has challenged these agencies to completely transform how they work—to become customer-oriented and results-driven to the extent the public will see a difference. This goal has been identified as one of the HHS reinvention goals. It involves partnering with other government and consumer organizations. It's easy to understand, it's measurable and the focus is on an outcome. This means it isn't a process or activity goal, but one that will have an impact on a specific target audience—the American public. Goals representing these qualities are what Congress wants to see in agency performance plans.

The Special Projects Staff in the Office of Management is now responsible for developing future performance plans for the Center. The process of identifying goals for fiscal year 2000 has begun. One of our jobs is to help Center managers develop goals that stretch CDER's role in contributing to the health of the American public. Goals must not only contribute to safe and effective drug products, but take further steps toward an expanded role in drug development, building partnerships and collaborating more with industry, the public and other invested parties. The goals must also be ones that everyone in CDER can share and understand his or her contribution toward their accomplishment. The tentative date for developing a draft plan is May. The final plan will be sent to Congress in October. Please check the OM Web site for updates.

Charlene Cherry is the Associate Director for Strategic Planning in the Office of Management.

FDA Launches Campaign To Help Women Use Medicines Wisely

With 30 percent to 50 percent of Americans not taking their medications as prescribed and the annual cost of preventable medicine-related illness estimated to be $76.6 billion, FDA launched a nationwide campaign to educate women about the importance of properly using medicines.

The grassroots campaign, Women's Health: Take Time to Care, is primarily directed at women over 45, particularly those who are under-served. The focus is specifically on women, because they often manage medications for their entire family as well as themselves. The campaign's information materials on the theme "Use Medicines Wisely" will help women learn more about important medication issues, including preventing interactions among drugs, following instructions, keeping track of medication regimens and getting professional advice.

"Not following a drug regimen can have serious consequences," said Lead Deputy Commissioner **Michael A. Friedman, M.D.** "The campaign's goal is to bring home the fact that medicines usually work best when taken as prescribed."

The FDA's Office of Women's Health partnered with the National Association of Chain Drug Stores and a broad network of consumer organizations, women's groups, health care providers, health institutions and government agencies to develop the campaign, including the League of Women Voters, American Heart Association, National Black Nurses Association and American Association for Retired Persons. The public awareness campaign includes a tour of 15 cities, which began last month in San Francisco. FDA also plans to bring the program to rural communities and Indian reservations.

Reviewer Affairs Corner

Reviewer's Handbook Earns Official Status

By Melissa Maust and Fred Marsik

It's official, the CDER *Reviewer's Handbook* (March *Pike),* prepared by the handbook subcommittee of the Reviewer Affairs Committee, has been approved. The work on this document began about two years ago, and the subcommittee for the Reviewer's Handbook dedicated a lot of time and effort to this endeavor.

A special thank you is extended to **Ferrin Harrison** and **Ross Pierce** and to the new chair, **C. Russ Rutledge** for their persistence, dedication and enthusiasm. Remember that this is a living document, and comments are welcome at any time.

The RAC representatives are currently in the process of distributing this handbook to all primary reviewers, and very soon the handbook will be on the Center's intranet. The next Reviewer Affairs Corner will feature the 1998 RAC representatives.

- *Other news from the RAC:* A task force has been developed to address issues that have arisen with the current *Proposal for the Enhancement of Multidisciplinary Team Approach to Review Submissions by the Project Management Coordinating Committee* (see e-mail from **Jean Yager** dated Feb. 3 or click on the blue text). This task force, led by **Raj Uppoor,** is actively preparing comments and suggestions on the proposal for submission to the Project Management Coordinating Committee on behalf of the Reviewer Affairs Committee.
- *Innovations recognition ceremony:* The RAC, on behalf of all the reviewers at CDER, thanks the Center's management and staff for providing the opportunity to celebrate the Innovations in American Government Award on March 3. The reviewers in CDER understand the importance to the health of the American people that the reforms in the approval process represent. The RAC and the reviewers it represents look forward to working with the management of CDER in its efforts to make further improvements to the drug approval process.

Melissa Maust is RAC chair and a chemist in OGD's Division of Chemistry 1. Fred Marsik in a microbiologist in ODE IV's Division of Anti-Infective Drug Products.

Leadership Fellows Corner

Intra-Agency Adverse Event Working Group Has Inaugural Meeting

By Nancy Haggard

One of CDER's transformation goals is to increase its collaborative and cooperative efforts with regulated industry and others within FDA. This calls on each of us to look at our own processes and how we could improve them by working with others.

As the post-marketing adverse drug reaction manager for the Office of Compliance, I recognized that FDA's other medical review centers have similar programs operating under similar regulations.

Sure, my colleagues in the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health and the Center for Veterinary Medicine were aware of each other. However, we didn't meet on a routine basis to share information or ideas on how we could improve our compliance processes or industry's compliance.

Part of my Leadership Fellows project was to start the ball rolling toward establishment of what is now known as the Intra-Agency Adverse Event Working Group. It wasn't as difficult to organize as I initially thought. Management at all three centers quickly saw the potential of collaborative efforts. Individuals involved with adverse event reporting were equally enthusiastic. During the first meeting, we explored a number of areas in which we can work together.

Members of the working group are: **Bill Calvert, Deanne Knapp** and myself from CDER; **Howard Press** and **Chester Reynolds** from CDRH; **Alice Godziemski** from CBER; and **Neal Batalier** from CVM.

Nancy Haggard is a consumer safety officer in the Division of Prescription Drug Compliance and Surveillance.

Famulare Heads Manufacturing and Product Quality in Compliance

Joseph C. Famulare has been appointed the new director of the Division of Manufacturing and Product Quality in the Office of Compliance. Famulare initially joined the division in January 1996 as the branch chief of the Case Management and Guidance Branch.

The branch is responsible for issuing current good manufacturing practice to FDA field offices and industry. It also processes all CGMP cases submitted by FDA field offices.

Famulare began his career with the FDA as a consumer safety officer in the New York District. In August 1982, he was promoted to resident in charge investigator in the Buffalo District. In December 1987, he was promoted to supervisory investigator in the New York District and later transferred in November 1993 to the Long Island resident post.

Much of Famulare's field work has been in the drug CGMP area. As an investigator, he performed many CGMP inspections of drug manufacturers in the New Jersey and Buffalo districts. In the New York District, he handled drug inspections as a supervisor, many of which were precedent-setting cases during the generic drug scandal.

CDER Approves First Oral Therapy for Erectile Dysfunction

The Division of Cardio-Renal Drug Products approved sildenafil, the first oral tablet to treat erectile dysfunction. Taken about an hour before anticipated sexual activity, sildenafil enhances the response to sexual stimulation. It led to at least some improvement in seven out of 10 men with erectile dysfunction compared to two of 10 improving on placebo. Erectile dysfunction, commonly called impotence, affects millions of men in the United States.

In clinical studies, sildenafil was assessed for its effect on the ability of men with erectile dysfunction to engage in sexual activity and, in many cases, specifically on the ability to achieve and maintain an erection sufficient for satisfactory sexual activity. It was evaluated primarily at doses of 25 mg, 50 mg and 100 mg in 21 randomized, double-blind, placebo-controlled trials of up to six months in duration.

Sildenafil was administered to more than 3,000 patients aged 19 to 87 years, with erectile dysfunction of various causes—organic, psychogenic and mixed—with a mean duration of five years. The drug demonstrated statistically significant improvement compared to placebo in all 21 studies.

The first in a new class of medications, sildenafil is a selective inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase type 5, or PDE5. Physiologically, sexual stimulation causes local release of nitric oxide in the corpus cavernosum. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate, or cGMP. This produces smooth muscle relaxation in the corpus cavernosum and allows inflow of blood. Sildenafil enhances the effect of nitric oxide by inhibiting PDE5, which is responsible for degradation of cGMP in the corpus cavernosum.

Sildenafil was effective in a broad range of patients, including those whose erectile dysfunction arose from diabetes mellitus, spinal cord injury, trans-urethral resection of the prostate or no known physical cause. It was used on patients with a history of coronary artery disease, hypertension, peripheral vascular disease, depression, coronary artery bypass graft, and in patients taking various drugs, including anti-depressants, anti-psychotics, anti-hypertensives and diuretics.

For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, the drug may be taken anywhere from one-half hour to 4 hours before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day.

The drug should not be used with organic nitrates such as nitroglycerin patches or sublingual tablets because the combination may lower blood pressure.

Sildenafil's side effects, when they occur, are usually mild and temporary. The most common side effects reported in clinical trials included headache, flushing, and upset stomach. Visual changes, such as mild and temporary changes in blue/green color perception or increased sensitivity to light, can occur.

A thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes and identify appropriate treatment. There is a degree of cardiac risk associated with sexual activity; therefore, physicians may wish to consider the cardiovascular status of their patients prior to initiating any treatment.

Review team members for the sildenafil application were: medical officer, **Norman Stockbridge, M.D., Ph.D.,** pharmacology, **Estela Barry, M.S., Thomas Papoian, Ph.D.,** and **Albert DeFelice, Ph.D.;** biopharmaceutics, **Patrick Marroum, Ph.D.;** statistics, **Kooros Mahjoob, Ph.D.;** chemistry, **J.V. Advani;** Division of Drug Marketing and Advertising, **Mark Askine;** Division of Scientific Investigations, **Antoine El Hage, Ph.D.;** establishment inspections, **Shirnette Ferguson;** project manager, **Gary Buehler;** division director, **Raymond Lipicky, M.D.;** and office director, **Robert Temple, M.D.**

Sildenafil is marketed under the trade name Viagra.

The clinical review of the studies, approval letter and labeling can be found on the Internet at:

http://www.fda.gov/cder/news/viagra.htm.

Sildenafil Documents Made Public on Same Day as Approval

By Nancy Smith

Because the Office of Training and Communications anticipated wide public interest in sildenafil, it was able to place the available information about the drug on CDER's Web site on the day of approval. This information included redacted reviews, the approval letter, the text of the draft labeling, a consumer information sheet, questions and answers for consumers and a link to the FDA talk paper. OTCOM hopes to establish sites similar to this for future approvals of new molecular entities and priority drugs; although, it will generally be done within two to four weeks after approval.

The OTCOM people who pulled this together on short notice were: **Linda Brophy,** the office's associate director who coordinated the overall effort; **Roy Castle, Erik Henrikson,** and **J. Santford Williams,** in Freedom of Information, who scanned and redacted the approval letter and review; **Laura Bradbard, Lori Frederick, Brenda Kiliany, Mary Kremzner, Barry Poole** and **Ellen Shapiro,** in the Division of Communications Management, who coordinated with the FDA's Press Office and wrote the consumer information and question-and-answer documents; and **Paul Stauffer** and **Carol Assouad,** from the Medical Library, who designed the Web page; decided on content; converted, formatted and posted documents; coordinated receipt of documents in useable formats; and assured the material had been reviewed and approved before posting.

Nancy Smith is OTCOM's Director.

Aims at Reducing Animal Testing

OTR Brings Promise of Artificial Intelligence to Toxicology

(Continued from page 1)

assessment of the potential toxicity of candidate molecules and conventional animal toxicology screening methods may be a rate limiting step in this process. Computational toxicology, which combines the advances in computer technology and toxicology databases, may be useful for screening large numbers of candidate compounds to identify those with favorable toxicology profiles for further animal testing. This approach may facilitate the drug development process and reduce animal testing.

OTR's structure activity relationship project aspires to provide rapid and reliable decision support information in situations in which toxicology data are either not available or inadequate. Computational toxicology is not a substitute for toxicology studies but an aid in identifying and prioritizing the degree and nature of probable risk based on the toxicological profile of chemically related compounds.

This OTR research is a collaboration with Dr. Gilles Klopman, professor of chemistry at Case Western Reserve University who is president of Multicase, Inc., a small Ohio-based software company. The project aims to expand and enhance the company's commercial software, the Multicase quantitative structure activity relationship program, to improve its ability to evaluate the toxicity of pharmaceuticals.

Multicase software reduces molecules to fragments of two to 10 atoms in length. It then statistically analyzes the relationships of these fragments to the biological activities associated with similar molecular fragments in the program's control data set. The ability of such a program to predict toxicity is dependent on the nature of the control data set. If the fragments from the test molecule are not represented in the control data set (poor coverage), a poor prediction results. This has been a major reason for the failure of such systems in the past.

OTR has enhanced the control data sets used by the Multicase software in many aspects. The OTR-Multicase carcinogenicity software modules incorporate:

- New and larger control data sets derived from a nonproprietary database developed by OTR of approximately 1,000 rodent carcinogenicity studies. The original Multicase carcinogenicity data sets used only data from the National Toxicology Program carcinogenicity studies which are deficient in drug molecules.
- Separate data sets for each study cell. Carcinogenicity studies in male and female rats and mice (four study cells) are generally required for chronically used drugs and each gender and species is considered one study cell. Separate software modules were created by OTR for male and female rats and male and female mice. In the original Multicase program, male and female rodent study results were pooled.
- Aspects of a human expert system, in the form of additional scaling factors for potency that are related to the "weight of evidence" employed by CDER in evaluating results of carcinogenicity studies. In this scheme, compounds that are transspecies, transgender multisite carcinogens will have the highest potency score. In the original Multicase program there was no accommodation for relative potency of carcinogenic effect and studies were considered either positive or negative.

The OTR has completed a beta test, and the system now has high coverage for drug molecules compared to the original Multicase software and significantly outperforms it in validation studies. The OTR-Multicase rodent carcinogenicity software modules will soon be available commercially, and reproductive and developmental toxicity modules are in development.

Computer-assisted toxicology prediction has long been used by the Environmental Protection Agency for regulatory decision support. The FDA Center for Food Safety and Applied Nutrition is currently evaluating the use of the OTR-Multicase software to meet an FDA Modernization Act review deadline requirement for indirect food additives.

At CDER, this software has been used to support regulatory decisions regarding further toxicity testing or purification when new contaminants are identified in a drug substance that were not present in material originally tested in toxicity studies.

Joseph F. Contrera is the director and Edwin Matthews is a toxicologist in the regulatory research and analysis program of the Office of Testing and Research.

Parklawn Classic to be Held April 24, Registration Closes April 23

(Continued from page 1)

R&W Store, Room 5-01.

The Classic has been endorsed by Lead Deputy Commissioner **Michael Friedman, M.D.,** and HHS Secretary **Donna Shalala**.

"All year, we protect and promote the public health in our offices, laboratories and at inspection sites," Friedman said. "But each spring, we have an opportunity to advance the public health by getting outdoors and doing our part to keep physically fit."

Shalala said she enthusiastically endorses the Classic and welcomes its recognition as a departmentwide health-promotion event. "The theme of this year's event, Celebrate in '98, was chosen to commemorate the bicentennial of the Public Health Service," she said.

"I am encouraging you to participate by walking, running, spectating or volunteering. I can think of few better opportunities to begin or continue a personal health and fitness program and to join with fellow HHS employees in a fun and festive atmosphere," Shalala said. "Please check with your supervisor to make sure you can be spared from your regular duties."

For more information, call the Classic hotline at 3-5340.

Bronwyn Collier is the special assistant in ODE III and safety coordinator for the Parklawn Classic.