news along the pike

Center for Drug Evaluation and Research

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Inside Story

Teamwork Leads to Withdrawal of Diet Drugs

By David Graham, M.D., M.P.H., and Lanh Green, R.Ph., M.P.H.

The Center's Office of Epidemiology and Biostatistics (OEB) played a pivotal role in assessing the scope of heart valve dysfunction associated with the popular diet drugs fenfluramine and dexfenfluramine. A scientific and medical investigation of the problem led to the Sept.15 voluntary withdrawal of both products by their sponsors. Teamwork and aggressive marshaling of CDER's epidemiological and medical resources were keys to uncovering the data to support the withdrawal. The cooperation and collaboration of other divisions within the Center, the Agency's MedWatch program, the Centers for Disease Control and Prevention, the National Institutes of Health, physicians in private practice, the Mayo Clinic, CDER's Cooperative Epidemiology Agreements and the manufacturers were critical to a timely public health action.

At the end of June, **Heidi Connolly, M.D.,**

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Center Surpasses FY '96 Goals for Drug Reviews

By Murray Lumpkin, M.D.

CDER has once again not only met, but exceeded, the review performance goals established by the Prescription Drug User Fee Act (PDUFA) of 1992. For the Fiscal Year 1996 submission cohort, the law called for 80 percent of original NDAs, resubmissions of original NDAs, efficacy supplements and manufacturing supplements to be reviewed and acted upon "on time." The Center is now well above the 80 percent mark for all four categories in the fiscal year cohort of applications and supplements that started Oct. 1, 1995. CDER is even on target to surpass the previous year's superlative performance in all four categories. Aug. 31 data were:

- **Original NDAs:** 86 percent of the 109 filed original NDAs were reviewed and acted upon on time. None has missed its due date yet. There are still 15 original NDAs pending, so we have the potential of being 100 percent on time. If the Center does achieve a 100 percent on-time performance, it will have demonstrated consistent improvement: 65 percent on time with the FY '93 cohort; 95 percent with the FY '94 cohort; and 98 percent with the FY '95 cohort. It would be the first time the Center met a 100 percent target for a cohort.

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Time Reporting to Kick Off for All Employees

By Charlene Cherry

Many CDER employees ask why they must report time spent on daily activities starting Fiscal Year 1998. The question is valid. You will be asked to report on how you use your time during a two-week period in each quarter. The first time reporting period will occur in November or December.

What is the reasoning for tracking and reporting our daily time when Quality of Worklife Initiatives stress the advantages of eliminating time clocks and supporting maxiflex schedules? We operate in an environment of powerful economic forces. We cannot be complacent. We need to demonstrate how we meet our mandated mission. Justifying resources and funding is paramount in the volatile environment in which we currently operate.

In an era of limited resources and funding, Congress, industry and the American public are asking us to improve and streamline our processes and to assume a greater degree of

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Joe's Notebook

Scientific Teamwork

> "When philosophers first began to investigate the natures of things, they discovered that there were certain impediments that had to be overcome if students were to learn expeditiously and not fall into error. Among others, there are these impediments. First, students do not understand how we can come to a knowledge of things outside ourselves, with what powers or kinds of knowing we do so, since they make no distinction between sense and intellect. Another impediment: the great multitude and confusion of things and the general obscurity of their natures. A last impediment: the defective way of human knowing and lack of knowledge of the methods whereby we come to grasp those natures."
>
> —Ludovico Carbone

The quote is from Carbone's textbook, *Introduction to Logic*, published in Venice in 1597. As our Italian Renaissance author points out, how we know things, how we come to differentiate an imagined connection from a real one and the methods we use to do so have occupied scientists and philosophers from ancient times to today. **David Graham** and **Lanh Green's** inside look at how the Center came to sort out and understand the dimensions of the heart valve dysfunction associated with two popular diet drugs is a case in point.

We don't know for certain if early modern scientists like Galileo and William Harvey used Carbone's textbook, but his work, incorporating what we now call the scientific method, was widely used and reflected Renaissance thinking on the subject. Galileo and Harvey were working on the major scientific problems of their day and did so with support from the government. But today's investigations rarely involve a lone scientist and the tools he or she can lay out on a table or poke through a window at the evening sky. As you read the diet drug story and perhaps examine the data for yourself on our Internet site, keep in mind CDER's transformation goals. You'll not only get a feel for the excitement of good science, but you'll also see instances of the CDER transformation in action.

A hallmark of great teams is that they take care of extraordinary business and still find the time to get the everyday job done. User fee deadlines didn't take a break while the Center was grappling with diet drugs and the other items in this issue. **Mac Lumpkin** is just bursting with pride over the Center's performance with the FY '96 cohort of submissions. "Each and everyone of you in CDER has contributed to this performance and are to be congratulated and sincerely thanked!" he writes. "I wanted to share this great news with all of you who have worked so hard and so long this year to achieve these results—even with the hiring freeze and other distractions. I think it is extremely important, especially at this time, that we take a moment to celebrate what has been accomplished this year and to commit ourselves to finishing the remaining applications in this cohort on time so that this year's performance will, in the end, be the best yet of the PDUFA program."

Examples of teamwork don't stop at the workplace. **Lana Pauls** makes her debut in the Pike with a story that reminds us we're part of the local community. If you don't have the opportunity to make a commitment of time like **Nancy Haggard,** remember the Combined Federal Campaign.

And one last thought: don't spend too much time patting yourself on the back, because I don't think **Charlene Cherry** has a back-patting category for time reporting.

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

Innovations Award—Nothing Succeeds Like Success

By Jim Morrison

With the many posters floating around the various CDER sites and the kudos coming our way, we in CDER have reason to be proud that we are the primary factor in FDA's being recognized as one of the finalists in the 1997 Innovations in American Government Award, sponsored by the Ford Foundation and Harvard's John F. Kennedy School of Government. Whether we wind up as winners or just finalists, we have won. In addition to the $20,000 prize already gained, we have achieved recognition as being in the vanguard of a new era in government.

When the CDER transformation was rolled out last year, many of you may remember that one of the exercises was to write a headline for the Washington Post of whatever date it was in the year 2000. There were quite a few people who suggested something like, "CDER Wins Malcolm Baldridge Award." Although the criteria are different for the Innovations in American Government Award, who among us would have predicted we would be finalists for such a prestigious award just one year later?

> ". . . this system that led to the Innovations Award can be scaled down to any working unit . . ."

It is just as important to analyze one's successes as well as one's failures (and it's a lot more enjoyable). The Innovations Award is based largely on our success with new drug reviews and in exceeding user fee goals. It is easy to say that the Prescription Drug User Fee Act (PDUFA), which authorized a hefty increase in resources to CDER and CBER, is the reason we performed in such an outstanding manner. But such an analysis would be superficial and only half right. If you look at the statistics, you will see that the time to first action on NDAs started to fall before we accrued benefits of any increase in resources.

Our review times fell initially because we set goals to which we were committed. Other aspects of the award, such as accelerated approvals, came about independently of either additional resources or PDUFA. In fact, one can find many examples of projects that are infused with additional resources but fail because they are poorly managed. So my analysis of our success leads me to conclude that progress comes from measuring critical processes of an organization (or better yet, measuring outcomes), setting strategic goals, finding better ways of doing the job and then implementing them. Incidentally, this is not my original idea. You will find exactly this prescription in every reengineering or management book and in the application for the Malcolm Baldridge Award. There is a lot of verbiage around these principles, but the message is basically the same.

What is the payoff in all this for those of us who are toiling in fields not fertilized by PDUFA funds? The answer is that this system that led to the Innovations Award can be scaled down to any working unit, even down to the individual working alone. If you don't have extra funds coming in to cover the expense of measuring what you do, that's OK; this system comes with a built-in resource benefit.

As you identify ways to do things better and faster, you gain more time. With extra time, you can measure other processes and save even more. As you become more efficient, you can actually do some of those things you always wanted to but couldn't because you didn't have the time. You will enjoy your work more. You will be noticed for your better work or faster service. You will start to get awards for your performance. You will be innovating. People and organizations will come to you for advice and use you as a benchmark of excellence.

Think about it. Are there things you do that could be done more efficiently and more effectively? After all, we work for an award winning, innovative organization. We have an image of excellence to uphold.

Jim Morrison is the Center's Ombudsman.

Reviewer Affairs Corner

Progress Reported on Survey, Reviewers' Handbook

By Karen Oliver

After taking the month of August off, the CDER Reviewer Affairs Committee convened Sept. 9 for their monthly meeting. **Harold Silver,** chairperson of the 1997 RAC Survey Task Force Subcommittee, reported that 311 surveys were returned and that the data entry for the survey has been completed. The analysis team has just begun its work. **Katherine Meaker** reported that the respondents represented a wide range of disciplines, with 20 percent having been at CDER for less than one year.

Although the analysis has not been completed, positive changes noted by the respondents were familiarity with the RAC, the Master Reviewer Program and access to the Internet. **Harold Silver** and **Karen Lechter** are now compiling all the hand-written comments on the survey, which were considerable in number. The RAC and the RAC Survey Task Force wish to thank all 311 survey responders. We look forward to presenting the statistical results to all the reviewers by the end of the year.

Ferrin Harrison, representing Reviewers' Handbook subcommittee, reported that the CDER Reviewers' Handbook will be distributed electronically to the RAC members for final comment. The handbook is designed as a resource, reference guide and aid to help reviewers survive and thrive in our unique environment. Next month, information will be shared on upcoming RAC elections.

Karen Oliver is a project manager in the Division of Gastrointestinal & Coagulation Drug Products.

FDA Issues 'Approvable' Letter to Celgene For Thalidomide

On Sept. 19, the FDA issued an "approvable" letter to Celgene Inc. for thalidomide as a treatment for a leprosy complication: the skin manifestations of erythema nodosum leprosum (ENL). ENL is a serious, severe complication of leprosy for which no good alternative therapies are presently available for many people with this disease.

Issuance of an approvable letter is one of several intermediate steps that can be taken by FDA during the drug review process. It does not mean that the drug is approved for marketing in the United States at this time.

This approvable letter means that the Agency has determined that the submitted clinical data demonstrate that the benefits of this product outweigh the known risks in the treatment of ENL when the product is used under tightly controlled medical supervision. However, before a final approval decision can be made, additional information, including the wording of the final labeling and the details of a restricted distribution control system, must be submitted by Celgene and reviewed and agreed upon by FDA. As announced by Celgene, the company and the FDA are in discussions at present about these further issues.

In this approvable action, FDA is acting under its authority to restrict distribution of a product that presents major safety concerns. The letter makes clear that, if this product reaches the stage of final approval in the United States, it will be under the restricted distribution requirements.

Thalidomide is well-known to cause severe birth defects. Because of this, FDA is committed to using every means possible, including restricted distribution, to minimize the chance that such will occur and to maximize the opportunities for health practitioners and patients to be made fully aware of the potential side effects of this product before they choose to use it. Celgene has announced that it agrees with this restricted distribution concept: as mentioned previously, the details are yet to be completely worked out.

Timing of further FDA action on this application is now dependent on Celgene's responses to the issues identified in the approvable letter and on the rapidity with which they and FDA can come to agreement on these issues.

FDA's action follows the recommendations made earlier this month by a majority of FDA's Dermatologic and Ophthalmic Advisory Committee, a panel of outside experts asked to consider this matter.

Thalidomide is a drug originally marketed as a sedative outside the United States from the 1950s to early 1960s, until it was linked with severe birth defects. In addition to causing serious fetal deformities, thalidomide has been associated with other adverse reactions, including peripheral neuropathy, a disorder that, in some patients, has resulted in permanent nerve damage. The product has never been approved for use in the United States.

In the past several years, much has been learned about thalidomide's potent ability to modify the response of the human immune system. By exploiting this good effect of thalidomide, interest has risen in both the medical research community and in many patient advocacy groups for increased testing of this product for use in several severe diseases, like ENL, that are mediated through the immune system and for which no other good therapies are presently available.

FDA Proposes Ban on Common OTC Laxative Ingredient

The FDA proposed on Sept. 2 to ban phenolphthalein, an ingredient widely used in over-the-counter (OTC) laxative drug products, because it may potentially cause cancer. The proposal, announced in the *Federal Register*, would require that products containing this ingredient either be reformulated or withdrawn from the market.

Because consumers have access to more than two dozen laxative products without this ingredient, CDER believes that phenolphthalein's benefits do not outweigh its risks. The Center is proposing to reclassify phenolphthalein as a Category II ingredient, one not generally recognized as "safe and effective." The proposal to reclassify phenolphthalein as unsafe is based on a review of animal carcinogenicity studies carried out by the National Institutes of Health's National Toxicology Program in Research Triangle Park, N.C.

The animal studies indicate a potential cancer risk to people who use this ingredient at higher than recommended doses or for extended periods of time. Specifically, the two-year studies showed that rats and mice fed high doses of phenolphthalein—approximately 50 to 100 times the recommended dose for humans—developed a variety of tumors.

Other studies have shown that when mice were fed high doses of phenolphthalein for six months at 30 times the recommended human dose, they also developed tumors as well as genetic damage.

Most manufacturers have recently announced reformulations of their products with other laxative ingredients. Consumers are advised to read OTC laxative drug product labels carefully to be informed of changes in the active ingredients. The Nonprescription Drug Manufacturers Association has adopted a voluntary program called "Flag the Label" to aid consumers in recognizing when major changes have occurred in OTC drug products. This flag on the label alerts consumers to read the new label information.

Within CDER, key players in the proposed ban on phenolphthalein were the Division of Over-the-Counter Drug Products (DOTCDP) and the Carcinogenicity Assessment Committee.

The Center's point of contact is **Cheryl Turner,** an interdisciplinary scientist and registered nurse in DOTCDP. A final regulation will be issued following a review of comments received during a 30-day comment period.

History Corner

A Startling Discovery on Eve of 1906 Act

By John Swann, Ph.D.

Second of four parts

The Drug Laboratory of the Bureau of Chemistry, the forerunner of the Center for Drug Evaluation and Research, was established before the Agency had a legislative fiat under the 1906 Food and Drugs Act to interdict adulterated and misbranded drugs. Harvey Wiley envisioned the Laboratory as a national clearinghouse for the improvement of pharmaceutical assays.

It was fortunate that Wiley established the Laboratory before the Bureau's regulatory mandate, because an enormous problem existed at the very heart of the Laboratory's ability to render accurate, reproducible analytical results. Soon after Lyman Kebler started as Laboratory Director in March 1903, he discovered that the Bureau's own stock of reagents was misbranded and substantially adulterated, a finding that shocked Wiley. Among other problems, zinc, hydrochloric acid and glycerin labeled as chemically pure were contaminated with arsenic. Chromic acid was laced with sodium sulfate, and what was labeled as potassium cyanide actually was sodium cyanide.

The Drug Laboratory examined over 700 of the Bureau's chemicals in the next two years. The magnitude of the problem at the Bureau led the Association of Official Agricultural Chemists (AOAC) to launch a national study of the quality of chemical reagents. The AOAC created the Committee on the Testing of Chemical Reagents, with Kebler as head. Though the Bureau seemed to be singularly blessed with a proliferation of adulterated and mislabeled chemicals, one common problem Kebler and his colleagues observed was the labeling of a reagent as chemically pure when it was of medicinal quality—or worse. He remained in charge of chemical reagent testing for the AOAC until the 1920s.

Another cooperative venture between the Drug Laboratory and the AOAC—involving the Committee on Drug Adulterations of the American Pharmaceutical Association as well—concerned the methodologies of pharmaceutical analyses. The APhA had been unsuccessful in securing cooperation to promote uniformity in assays, and even some U.S. Pharmacopoeia (USP) assays had problems in reproducibility.

Kebler and the Drug Laboratory again led this effort. He was able to recruit assistance from workers representing many different types of institutions—pharmacy schools, universities, manufacturers, boards of health and boards of pharmacy. For the first two to three years, Kebler and his colleagues worked exclusively on assays of opium for morphine, largely because of the therapeutic importance of this drug and inconsistencies with some of the analytical methods. By 1905, the venture included a study of competing assays of cinchona, ipecac and nux vomica for the principal alkaloids of each. The following year they included aconite, belladonna, coca and colchicum. While USP assays yielded more uniform results with some drugs, other methods had more consistent results for other drugs.

These were detailed, extremely laborious procedures, but necessary. From a therapeutic standpoint, a practitioner had to know how much active ingredient was in a crude drug. From a legal standpoint (after 1906), once the Bureau was able to proceed against violative products, an erratic method of assay might not hold up well in court. Official USP procedures therefore had to produce results as uniform as possible.

The early work of the Drug Laboratory prior to the 1906 act was not entirely devoted to such technical studies. Kebler also wrote about problems in the drug supply for a popular audience, much in the same spirit as his supervisor. The head of the Laboratory drew on his industry experience when he wrote of tricks in the trade to supply adulterated pharmaceuticals.

In addition, he exposed efforts to foist upon the public bat oil, mermaid's oil, hair restorers, tuberculosis cures, porcupine oil, cures for lost manhood, obesity cures and other such concoctions. Knaves were always ready to create or fill a demand, no matter how spurious the product. The 1906 act brought some of this under control, and the nature of the Drug Laboratory's work expanded concomitantly—and with it the organization of what had been virtually a one-man show. It would be the first of dozens of reorganizations of the drug function within FDA.

John Swann is a historian in the FDA's History Office.

Pediatrics Corner

Volunteer Team Targets Rapid, Expert Response to Reviewers

By Khyati Roberts

The Pediatric Subcommittee announces the formation of a rapid response team on Oct. 1, to assist reviewers on pediatric issues on a day-to-day basis. The team will consist of two to three members from the Pediatric Subcommittee on a rotating basis along with the Chair of the Pediatric Subcommittee, **Rosemary Roberts, M.D.,** and the facilitator of the subcommittee, **Paula Botstein, M.D.** Rotating members will volunteer for three months at a time. The team will provide expert advice to reviewers on issues related to pediatric drug development. The team will strive to answer questions in a timely fashion with a one- to two-week turnaround time.

A block of time has been reserved for the rapid-response team to meet and discuss any issues, if needed. This meeting may also be used as a forum to present an issue to the team. All questions for the team should be directed to **Khyati Roberts** (HFD-6; ROBERTSK) who will forward the question to the SWAT team for action.

Khyati Roberts is project manager for the CDER Pediatric Subcommittee.

Leadership Fellows Corner

Using New Information Technology to Accomplish Results

By Tim Ames

A little over a year ago the first group of CDER leadership fellows were charged to develop and work toward accomplishing a "result" that would make a significant difference to them, to CDER and to society. No small task considering this was all to be realized in nine months. But working toward a result is a compelling, powerful force that can provide us with new focus about who we are and the work we do.

As a pharmacist and in the Office of Generic Drugs, I have often been amazed and frustrated by people's seeming lack of confidence in generic drug products. In my experience, even well-educated health care professionals have seemed biased in favor of the more expensive brand-name products. Believing this misperception to be detrimental to the public's health, not to mention its pocketbook, I chose to work toward this result: To improve the American public health by:

- Bringing quality generic drug products to market more rapidly.
- Increasing the public's confidence and knowledge about generic drug products.

The action I hoped would accomplish this result was to develop an Office of Generic Drugs World Wide Web homepage in conjunction with the input from the generic drug industry. Thus, by creating a means both to provide useful information to the generic drug industry and to educate the public about the comprehensive generic drug review process, I expected to accomplish my result. I also expected to make my result significant to CDER by aligning my result and action with two of CDER's transformation goals.

- To work collaboratively and cooperatively with industry.
- To develop and implement new information management and technology into all activities.

To make our homepage meaningful for the generic industry, I solicited input from several generic drug trade associations. I did this by contacting the executive directors of these organizations, explaining my project and requesting their assistance by providing me with input from their member generic drug firms on the types of information that would be useful to them in facilitating generic drug approvals. Each representative was enthusiastic about providing input. Many of their suggestions have been incorporated into our homepage. By enrolling them as stakeholders in my project, it not only broadened the circle of support but also increased open communications between our office and industry.

To improve the public's confidence in generic products, I created a thorough description of the generic drug review process in the form of a flow chart with extensive explanations of the actions that occur during the process. I hope that this information will provide assurance to the public that only high-quality generic drug products are approved for use by consumers and health care professionals.

Though my project has not been without barriers or resistance, I am happy to report that the Office of Generic Drugs homepage is due to be launched in the very near future. At that point I can look forward to evaluating its impact at accomplishing my result. I hope that you will have a chance to visit our page and encourage your comments and suggestions.

Tim Ames is a pharmacist in the Office of Generic Drugs.

24 New Leadership Fellows Picked

CDER announced the selection of its 25 Leadership Fellows for 1997-98. These Center employees will participate, along with other government employees, in a rigorous leadership development program sponsored by the Council for Excellence in Government. Congratulations are due to the following:

Tracy Acker, Girish A. Aras, Steven Aurecchia, Edward Dennis Bashaw, Raman Baweja, Celeste Bove, Sonia C. Castillo, Rose E. Cunningham, Patricia DeSantis, Bonnie B. Dunn, Elaine Frost, Nancy Haggard, Barbara Ann Hill, Steven Hirschfeld, Chin Chang Koerner, Antonis D. Koutsoukos, Saul Malozowski, Corrine Moody, Lana Pauls, Radkika Rajagopalan, Bob A. Rappaport, Kellie Schoolar Reynolds, Linda J. Utrup, Celia Jaffe Winchell.

OIT to Make Computer Documentation Available on Intranet Web Site

By Raye Parker

Have you ever asked, "I know we did that in class, but I can't remember how to do it now." Or, "What do you mean, M:\drive?" Do people always ask you questions about CDER's network or applications? Or, are you the one who always seems to have questions? It is often said that knowledge is not knowing the answers to all the questions, but in knowing where to go to get the answers.

The Office of Information Technology (OIT) recently focused several months of concentrated efforts to ensure that you can get answers to some of your questions about the computer systems, applications and databases used at CDER. This documentation will be available on OIT's new intranet Web site. The Documentation area of the OIT Web will contain several categories such as CDER Trifolds, IT MaPPs and Applications Training Documentation. CDER Trifolds provide access to those handy "cheat sheets" on popular software packages. Procedures for selecting computer hardware, posting information on CDER's World Wide Web and policies for the Information Technology Coordinating Committee (ITCC) are all in the IT MaPPs area.

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EEO Corner

CDER Employees Contribute to Hispanic Celebration

By Gloria Marquez Sundaresan

"My fellow Americans, we must never, ever believe that our diversity is a weakness—it is our greatest strength," said President Clinton during his 1997 State of the Union Address. Indeed, we as a nation have become more diverse in society as well as in the workforce. Hispanics are part of this diversity, and their contributions helped make this country and maintain its standing in the world of nations in matters of peace, security and economic strength.

A Hispanic is a person who has origins among any of the peoples of Mexico, Puerto Rico, Cuba, Central or South America or has other Spanish culture regardless of race. From Sept. 15 to Oct. 15 of each year, the nation celebrates the National Hispanic Heritage Month by Presidential proclamation. Originally, this event was observed for one week, but in 1989 it was changed to a month of celebration.

In CDER, we celebrate this event with a display of notable Hispanics in the 5th floor, B-wing lobby of the Parklawn Building. In addition, a videconference between the Parklawn and Corporate buildings took place Sept. 17. This event was sponsored by CDER EEO Information Training and Sharing Satellites (CEISATS), and the focus was on the Hispanic culture.

Guest speakers were: **Carlos Manduley, Ph.D.,** Montgomery County Government, and **Marlene Swider, M.H.S.A.,** Office of Regulatory Affairs. Both speakers were interviewed after their talks.

Dannette Locklear, ODE II, demonstrated her favorite recipe and invited guests to sample it. The presentation was arranged like a variety show, and **Evelyn Farinas,** OEB, moderated. The film, "Drumbeats from the Americas," had examples of drum music from the various Central American countries. The performer then created his own united drumbeat for all the Americas.

Other participants included: **Nancy Haggard** who discussed Hispanic representation in the sciences; cultural news was reported by **Hector Zuazua**; **Noreen Gomez,** EEO, discussed cultural festivities from Trinidad and Tobago; **Ana Szarfman,** OEB, was part of the production committee; **Kathy Abel,** OCPB, talked about Hispanic chartered schools; and **Dorothy Menelas,** OTR, discussed the historical and cultural places of South America in her talk "Jewels of South America."

Special thanks go to OTCOM's **Wendy Stanfield, Angie Youngblood,** and **Wanda Clabaugh,** who is also vicechair of the EEO council.

Gloria Marquez Sundaresan is an EEO specialist in the Center's EEO Staff.

FDA Employees Donate Facilitation Skills to County Latino Program

By Lana Pauls

The Office of Compliance's **Nancy Haggard** and her husband, **David Haggard,** along with **Hector Zuazua,** who are both from the Agency's Office of Regulatory Affairs, donated their time to the Latino community of Montgomery County, Maryland, by providing group facilitation skills to the county's Latino Visioning Day. The event was held on Saturday, Aug. 9, at the Holiday Park Elder Center in Wheaton.

"About 50 or 60 people showed up," Nancy Haggard said, "and we broke them into small groups. We tried to guide the groups to address the main issues and make sure they didn't deviate from the main topics. At the end, a spokesperson for each group presented the ideas that were developed."

The purpose of the day-long meeting was to generate community consensus on the best means to make a dramatic improvement in the quality of life for Latinos in Montgomery County in the areas of housing, health, social services, education and economic development.

The Montgomery County Concejo Latino (MCCL), a non-profit organization, was incorporated as a result of the event. The MCCL will immediately proceed to develop two comprehensive Latino Community Centers in Montgomery County, as well as to develop high-quality social service programming for Latino residents of the County.

Lana Pauls is a supervisory consumer safety officer in the Division of Reproductive and Urologic Drug Products.

Documentation on Popular Applications to be Available on Intranet

(Continued from page 6)

The Applications Training Documentation part of the OIT Web contains all the manuals, handouts and Quick Reference Cards provided in the current OIT classes such as Microsoft Office Applications (Windows 95, Word, Excel, Access and PowerPoint) as well as Excalibur, TeamLinks, Russell Calendar Manager and Local Area Network (LAN). Manuals for less frequently taught classes, such as ALL-IN-1 and SmarTerm, are also included in this area. Applications training documents are available in a variety of formats. HTML format allows you to quickly view the material for answers to Frequently Asked Questions (FAQs) and MS Word format allows you to get a formal hardcopy of a manual. Now, in order to be super-prepared, you can have a copy of the manual prior to attending class. Information in the Documentation area will constantly grow. Documentation on the infrastructure and applications areas is being finalized now and will be added in the near future. You can find the site at: http://oitweb/oit.

Raye Parker is a computer specialist in the Technology Services Support Staff.

Project Management Corner

Scientific Excellence, Rapid Development Goals Merge

By Deborah Kallgren

Charles Grudzinskas, vice president for medications and project management at G.D. Searle and Co. kicked off the fall CDER seminar series Sept. 3 with a talk entitled "Project Management: Merging the Goals of Excellence and Velocity." Over the past decade, the drug development cycle from discovery to NDA approval has been reduced from an average of eight to 10 years to four to six years. Grudzinskas noted that the time between the first human study and licensing submissions has been reduced to less than four years in both the United States and Europe. Grudzinskas identified four key changes to development processes that have impacted favorably on cycle times.

- *Impact of managed health care.* "Now, there is a greater need than ever to identify ways to shorten the time to developing new products," Grudzinskas said. But how do you get it "right" and "fast" at the same time? Ultimately, it is more economical for industry to produce high quality NDAs from the start, than to rework poorer quality NDAs. According to FDA assessments, industry is now submitting more fileable applications, making fewer major amendments and more rapid resubmissions after a first action.
- *FDA access and advice.* Open lines of formal and informal communication between FDA and industry are a necessity during the drug development and review process. Industry has stepped up its collaboration with the FDA, sharing information about new product strategies, projects in the pipeline and its decision-making rationale. A further example of collaboration is the Joint FDA/DIA (Drug Information Association) Project Management Training Workshop scheduled for Oct. 29-31, in Washington, D.C. The primary objective of this workshop is to provide interactive, learning opportunities for Agency and industry project managers and regulatory affairs professionals. For more information about the workshop, see the August issue of *News Along the Pike.*
- *Strategic planning.* Development of a strategic plan involves designing a portfolio that characterizes the drug, understanding how to assess drug candidates and the competitive environment, charting the probability that the product will meet all the hurdles, identifying key value drivers and having clear expectations of costs involved for development. The most critical element is designing well-controlled studies to produce quality data and scientific rigor.
- *Integrated drug development team.* Industry teams must be able to manage and understand a wide variety of interdisciplinary scientific issues that arise during the development of new products. The more diverse the pool of expertise, the stronger the resources available to that team. Strong teams have a clear grasp of project objectives and decision-making criteria. "Before a project is initiated, the first thing each team must do is agree upon what method they will use to make decisions, and how those decisions will be communicated back to management," Grudzinskas said. It is important to remember that teams benefit most from their participation in the decision-making process.

Deborah Kallgren is a project manager in the Office of the Center Director.

Information Technology Corner

CDER Unveils Electronic Document Room

By Mark Gonitzke

A New Drug Application (NDA) is delivered in hundreds of boxes requiring fork lifts to move. CDER pays millions of dollars each year to store, transport and use this information during the review process. To improve information access and cut costs, the Office of Information Technology has established the Electronic Document Room (EDR) to receive, process and archive electronic submissions. This will start with the Case Report Forms and Case Report Tabulations sections of the NDA. These two sections alone make up 50 percent to 75 percent of the average NDA. This capability will be extended to the remaining NDA sections as soon as possible.

Moving bits of computer data is faster, less expensive and provides better access than moving the atoms of paper—up to 20,000 pages can fit on a CD-ROM disk; an entire submission can fit on a single computer tape cartridge. The EDR will enable CDER to maintain the archival copy of regulatory submissions so that years from now the data can be located and reviewed without sorting through huge warehouses of paper.

To ensure that sponsors understand the file formats and other specifics for electronic documents and data that the EDR is prepared to archive and provide a read-only copy to reviewers, CDER has issued a guidance for industry, *Archiving Submissions in Electronic Format—NDAs.*

Currently this guidance document only includes the specifications for Section 1, the Index (NDA Table of Contents); Section 11, Case Report Tabulations; and Section 12, Case Report Forms. However, each of the 19 sections covered in the application form will eventually be included in the guidance document.

The EDR is located at CDER's Central Document Room and will process all submissions that contain electronic sections that are identified in guidance. The EDR staff will separate the electronic media from the paper, upload the electronic portion to a server, check that portion for usability and conformance to the guidance, and enter all relevant data into COMIS (Center-wide ORACLE Information Management System). The staff will

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Exec Sec Handles "Dear CDER" Mailbag

By Pam Fagelson

When the average American consumer writes a "Dear FDA" letter about a human drug, chances are it will find its way to CDER's Executive Secretariat Team. Once there, **Lee Zwanziger** and her staff have the task of crafting a suitable and official reply. The variety of these letters is limitless and, though some evoke a chuckle and others a tear, each is given personal and prompt attention. A recent perusal of the CDER mailbag turned up suggestions for new indications (for example, anti-depressants for prevention of colds), expressions of concern about mare's urine and Premarin, a letter from the bereaved father of a child who died of an allergic reaction and a multi-page thank-you letter from a citizen amazed and delighted to have received a response to his letter from Center Director **Janet Woodcock, M.D.** People frequently write about side effects of their medications that they did not expect, drug prices or reimbursement policies, concerns about the conduct of a particular health-care provider and suggestions urging the immediate approval or withdrawal of any number of specific drug products.

"The Exec Sec Team, a low-key and unsung part of the Executive Operations Staff, is charged with managing all correspondence and mail into and out of the Office of the Center Director . . . "

The Exec Sec Team, a low-key and unsung part of the Executive Operations Staff, is charged with managing all correspondence and mail into and out of the Office of the Center Director, as well as correspondence addressed personally to Janet Woodcock. Most CDER mail not addressed directly to someone else arrives in the Executive Secretariat. Strongly focused as a service operation for the Center and the public, the Exec Sec Team directly answers the bulk of consumer mail with the goal of a two-week response time. They also log and track other correspondence such as draft letters responding to inquiries from members of Congress.

A typical day starts with a short all-hands meeting to divide up the e-mail that has arrived overnight and to get a briefing on announcements, updates or hot items. The Exec Sec Team works closely with the Agency's Offices of Legislative Affairs, Financial Management, Consumer Affairs and its own Executive Secretariat to coordinate the flow of CDER-related responses out of FDA and the Center.

During the course of the day, the e-mail account will be checked at least four times for information requests from Agency offices, and the staff will meet informally to keep everyone aware of late-breaking topics and the status of projects and correspondence. The skills of seven staff members with expertise in consumer issues, science, legislation, policy and information management are focused on responding to the many written questions and comments received at the Center, averaging more than 200 a month.

As many responses as possible are developed individually by the team, based on their knowledge of the topic and publicly releasable information. All replies are reviewed by the team leader and higher level officers as needed before being sent out. Overall, very few inquiries are referred to divisions, which the team notes is due in part to office and division contacts who are extremely helpful in providing information and teaching the Exec Sec Team about issues that arise. Lee emphasizes service to the internal customer when she talks about the "importance of doing what we can to help the divisions so that they can do what they do best."

Congressional inquiries and requests for comments are also tracked and distributed appropriately for response. Team members collect and assemble CDER's official response to these "congressionals" to ensure consistency and adherence to priority deadlines. The Exec Sec Team works closely with the drug information group in OTCOM that manages the CDER phone lines, and they all pitch in when CDER is deluged by write-in campaigns such as the recent ones for Myotrophin and Premarin. OTCOM's drug information group makes sure that each writer in these campaigns receives an appropriate and individual response.

In addition, Exec Sec Team members, like other members of the Executive Operations Staff, individually provide information management and project management services on various issues for a variety of working groups. The close-knit and information-sharing environment of the office enables the staff to provide continuity of service to these committees even though the staff members may change over time.

On a weekly basis, the Exec Sec Team provides the Office of the Commissioner with a list of hot topics for HHS, the White House and senior managers. Exec Sec is presently working on ways to expand the collecting and sharing of such data without increasing the reporting burden of the programs.

Through their prompt and responsible management of CDER's correspondence, the staff and leadership of the CDER Executive Secretariat Team provides a fine example of service to both internal and external customers.

Pam Fagelson is a management analyst in the Office of Management.

Electronic Document Room Unveiled

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create two archival tapes, move the electronic portion to a server near the review division and send notifications to review team project managers. Then reviewers can use the Microsoft Internet Explorer to locate the data they want for review.

To learn more about the Electronic Document Room, contact me (7-5478, e-mail GONITZKE). The guidance is available at: http://www.fda.gov/cder/guidance/arcguide.pdf.

Mark Gonitzke is a member of the Division of Data Management Services.

Scientific Teamwork Emphasized in Diet Drug Analysis

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of the Mayo Clinic contacted FDA. Her article detailing 24 cases of cardiac valvular disease associated with the fenfluramine and phentermine had been accepted for publication by the *New England Journal of Medicine.* Because of the public health implications of her findings, the journal had waived its normal embargo on a prepublication announcement. **Murray Lumpkin, M.D.,** Deputy Center Director (Review Management), brought the relevant groups together and mobilized the resources of the Center for a coordinated response.

On July 8, the Mayo Clinic and FDA went public with their information. FDA issued a Public Health Advisory to 700,000 health care practitioners and institutions requesting that case reports of similar problems associated with these drugs be submitted to MedWatch, including information on echocardiograms that may have been performed. The echocardiogram was a critical piece of information that could be used to classify a patient report as describing valvular dysfunction.

Shortly after, Dr. Lumpkin established a task force with representatives from OEB's Division of Pharmocovigilance and Epidemiology (DPE), ODE II's Division of Metabolic and Endocrine Drug Products (DMEDP), ODE I's Division of Cardio Renal Drug Products (DCRDP), MedWatch, Office of Training and Communications, Office of General Counsel, Office of the Commissioner, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH).

The operation was divided into two phases. Phase one centered around the public health advisory and strategies to deal with the expected flurry of reporting to MedWatch by physicians. Phase two involved the scientific and medical efforts required to go beyond assessment of the case reports in order to determine if the reported cases were related to exposure to the appetite suppressants or to other factors. Among our major tasks, we needed to:

- Develop a research definition of a "case."
- Estimate the exposure patterns of each of the drugs alone and in combination.
- Estimate the incidence rates of valvulopathy.
- Assess risk factors.
- Estimate the potential impact in the population.
- Identify possible control groups to determine if the problem was occurring more often than expected.

Such data would contribute to the Center's information needs and help guide public health decision-making. **David Graham, M.D., M.P.H.,** a medical officer in DPE, and **Bruce Stadel, M.D., M.P.H.,** a medical officer in DMEDP, were asked to spearhead this second phase.

An important early step in the investigation involved understanding how and to what extent these appetite suppressant drugs were used. CDER is fortunate to have a number of external resources available to address these issues in a timely manner. One such resource is access to drug-use data from IMS America, a commercial provider.

Diane Wysowski, Ph.D., an epidemiologist in DPE, extracted all the relevant data and analyzed it for trends and demographic patterns. She found that fenfluramine was almost always prescribed with phentermine while dexfenfluramine was more often prescribed as monotherapy. In addition, her analyses showed that most of the product use was in women and in people below age 60. This information was critical to our interpretation of case reports because it helped explain why nearly all MedWatch reports of valvular dysfunction were in women and why only a few reports were received with fenfluramine used alone.

We had to organize the case reports that were being received in a way that was most useful for future analysis and potential queries. **Lanh Green, R.Ph., M.P.H.,** in the Reports Evaluation Branch of DPE, worked together with Dr. Graham to design and set up a customized database. We agreed on a process in which our MedWatch colleagues would immediately fax a copy of a MedWatch report to us and then send the original through the regular system. This enabled us to accumulate a database in a very timely manner. With the agreement of DMEDP, we contacted the sponsors of the drugs and requested they report to us several times a week and fax us any case reports they received.

At the beginning of August, we had slightly more than 30 case reports and, by the end of August, the number had grown to 65. These reports were in addition to the Mayo Clinic's 24 cases. On Aug. 28, the *New England Journal of Medicine* published the Mayo Clinic experience along with a letter to the editor from Lanh Green and David Graham providing our evaluation of 28 case reports that we had received through the end of July.

We now had enough case reports to develop a "research" case definition that was used to separate patients with abnormal findings from patients with minor dysfunction that might represent normal background. From a review of all our reports, we concluded that this disorder seemed primarily to affect valves on the left side of the heart. These findings were presented to the task force who were instrumental in formulating our final case definition—aortic regurgitation of mild or greater severity and/or mitral regurgitation of moderate to greater severity based on echocardiogram.

Equipped with this case definition, we could then look at how often patients might be identified with this problem in the population at large and, more specifically, in the population that was taking these drugs. There were many unknowns:

- Was it a problem of the drugs used by themselves or just in combination?
- Was it associated with the dosage or duration of drug use?
- Was it a rare finding or associated with improved echocardiographic technology?
- What was the proportion of symptomatic to asymptomatic patients?

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OEB's Special Tools Key to Uncovering Scope of Problem

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Another resource available to our division is the Cooperative Agreement Program in Pharmacoepidemiology through which we provide funding for seven research groups around the country. These groups each have principal investigators with whom we collaborate and large population-based record-linked databases. We have timely access to computerized data of prescription drugs and diagnoses received by large populations of patients in the course of their routine medical care. Shortly after FDA's July 8 Public Health Advisory, we sent out a request to each of our Cooperative Agreement Programs to see how many users of appetite suppressants they had.

Over the next two to three weeks, each program came back with the number of patients they had in their databases. Two databases had information we thought we could use. In one, it was technically feasible to start a study immediately. Those data are identified on CDER's Web site as "Epidemiologic Study of Valvulopathy with Fenfluramine Use in an HMO."

"This episode illustrates the value added to public health safety assessment by an active postmarketing safety and epidemiology staff."

We asked the investigator to create a file of all patients treated with appetite suppressant drugs and to identify those who had received echocardiograms. Within a matter of weeks we had our first population-based evidence that the valvular problem might be real. In this HMO, we identified 935 people who had been prescribed fenfluramine, of whom 34 had received echocardiograms for routine health care reasons. Of those echocardiograms, 25 were performed before these patients took appetite suppressants, and nine were performed after starting to use these drugs. No abnormal echocardiograms were found on the 25 patients tested before treatment started. Four of the nine echocardiograms performed after starting the drugs were abnormal using our case definition.

These population-based results were important information to addressing several major concerns. One of the concerns was whether the valvular disease could be due to obesity itself. Having 25 obese patients with echocardiograms before taking the drug gave us real insight into what the background risk of valvular dysfunction might be in this subpopulation. In addition, the finding of such a high proportion with the abnormality among the group with cardiac echocardiograms after starting diet drugs, represented a signal that was consistent with other data we subsequently secured.

We presented these data at a meeting of the task force on Aug. 28. At this same meeting, the National Institute of Digestive and Kidney Diseases shared with the group preliminary data from an echocardiographic prevalence study of patients treated with fenfluramine and phentermine that her institute was sponsoring. We were told that about 20 percent of asymptomatic patients undergoing echocardiography in that study had aortic regurgitation.

In early September, a Florida physician made us aware that he was finding a high rate of echocardiographic abnormalities in his asymptomatic patients. As we conferred with him over the next several days, he gave us contacts with other physicians in the weight loss community who were also performing echocardiograms on their patients. Through this informal network, we were able to identify five researchers around the country who had done echocardiograms on their asymptomatic patients.

Based on IMS drug-use data, between 1 million and 2 million people had probably been exposed to these drugs, and we thought there might be at least a 20 percent risk of cardiac valvular dysfunction in patients treated with these products. We believed most were probably asymptomatic. **Jim Bilstad, M.D,** Director, ODE II, and **Sol Sobel, M.D.,** Director, DMEDP, helped coordinate the next phase of intensive activity. We were joined in this effort by **Steve Rodin, M.D.**, a medical officer in ODE I's Division of Cardio-Renal Drug Products, as we focused on establishing estimates of the background rates of aortic and mitral valvular regurgitation and on assessing the technological issues surrounding echocardiography.

Also at this time, we began to receive summarized data from the five researchers, each from a different site. We now had to examine the consistency of the estimates of risk of "caseness" across all data sets, account for the statistical uncertainty of the estimates and estimate the absolute and relative risks for valvular disease. **Yi Tsong, Ph.D.**, from OEB's Division of Biostatistics III was a major help. He performed a sensitivity analysis of the data to determine how likely it would be that all five of our data sets would have such high observed case rates, assuming different background rates. The results we had were determined unlikely to be a chance occurrence. We presented our analyses internally and to the companies. The sponsors withdrew fenfluramine and dexfenfluramine.

This episode illustrates the value added to public health safety assessment by an active postmarketing safety and epidemiology staff. It also demonstrates the necessity of having timely access to current data on drug exposures and outcomes from multiple different sources in order to address responsibly and quickly important drug safety concerns. These events also emphasize the value of teamwork within CDER and our active posture in the interest of the public health.

You can find the data and other information on the Web at:
http://www.fda.gov/cder/news/feninfo.htm.

David Graham is a medical officer and Lanh Green is a postmarketing safety evaluator in the Division of Pharmacovigilance and Epidemiology.

Center Exceeds PDUFA's FY '96 Review Performance Goals

(Continued from page 1)

- **Resubmissions of original NDAs:** 99 percent of the resubmissions of original NDAs were on time. Because all the submissions in this group have been acted upon, the 99 percent on-time figure is final. There were 89 applications in this group, and the Center reviewed and acted upon 88 of them within the 6 months agreed under PDUFA. This also shows consistent improvement: 83 percent were on time with the FY '94 cohort, and 97 percent with the FY '95 cohort.
- **Efficacy supplements:** 94 percent were on time. The Center has missed its target date on two of the 106 supplements. There are still four pending, so the potential is for 98 percent on-time performance. If these are reviewed on time, CDER would again continue to show consistent improvement: 41 percent with the FY '93; 77 percent with the FY '94 cohort; and 95 percent with the FY '95 cohort.
- **Manufacturing supplements:** The numbers alone speak eloquently of the superior performance of CDER's chemists and microbiologists. All 1,218 manufacturing supplements in this cohort have now been reviewed and acted upon—96 percent in the on-time six-month period agreed to under PDUFA. This also shows consistent improvement: 50 percent on time with the FY '93 cohort; 66 percent with the FY '94 cohort; and 90 percent with the FY '95 cohort.

Murray Lumpkin is Deputy Center Director (Review Management).

Two-Week Time Reporting Period to Include All Employees

(Continued from page 1)

accountability in accomplishing our mandate. Different areas of our mission reach critical mass at different times. Knowing the amount of time spent on work activities and where efforts are expended will give management flexibility to prioritize and assign resources to critical areas.

The data derived from time reporting will enable management to give quantifiable answers to questions posed by Congress, industry and other external stakeholders. Time reporting will also enable the short-term and strategic planning required by management initiatives that include the Government Performance and Results Act (GPRA) and the Information Technology Management Reform Act (ITMRA).

Time reporting is not a new concept. Private industry has been doing it for years. Many government organizations including other centers in FDA time report. PDUFA provided the impetus for development of the current time reporting system in CDER. This system broadly tracks PDUFA activities and is done in the review divisions only. It is limited to 10 categories and reporting is done for a two-week period each quarter.

Current legislation in Congress, namely the FDA Modernization and Accountability Act of 1997 (FDA Reform) and PDUFA II, is expected to place new and expanded requirements on CDER. In the future, we will be required to report our performance to OMB and Congress in quantifiable measures. For example, premarket review activities, supporting research, education and information technology areas have all been identified as critical program elements that have specific goals targeted under GPRA. Premarket is the only area for which we can currently provide data, and that can be done only in broad, limited measures.

The new time reporting system expands the current system from 10 categories to almost 200. Categories are structured under five major classifications:

- Premarket review includes all IND, NDA and ANDA related activities.
- Postmarket review includes supplement reviews, pharmacovigilance and epidemiology, Phase IV and compliance actions.
- External leverage incorporates all activities that have an impact outside the Center—scientific and regulatory guidance, ICH, SUPAC and FOI.
- Internal capacity is the nuts and bolts of Center operations—IT support, supervisory duties, administrative, personnel, facilities, budget, management analysis, training and travel.
- Oversight includes all legislative interactions, GAO and IG activities and PDUFA negotiation.

Time reporting contacts in each division and staff will be identified. Contacts will receive training on the system and they in turn will train others in their divisions. They will also act as liaisons with the Office of Management during time reporting periods.

Although 200 time reported categories may appear daunting, most of us will be reporting on an average of five to six categories. The 200 categories encompass all activities performed in the Center.

The system will become operational on Oct. 1 through an automated online system accessible through a menu choice in Smarterm. After you enter your identification number, the system provides all other relevant information about you such as your name and division. There will be areas for you to record your activity information, which the screen will automatically tabulate.

People from all areas of the Center are currently testing the system. We are using their feedback to make it as user-friendly as possible. Training of contacts will take place during late September and October. Everyone should be able to operate the system by mid-November. Comments and suggestions may be addressed to the Time Reporting e-mail account, TIME_REPORT, or to any member of the time reporting team: **Charlene Cherry** (CHERRYC), **Richard Allen** (ALLENR), **Anne Henig** (HENIGA), **Kristin Crown** (CROWNK), **Dan Luckabaugh** (LUCKABAUGH), **Vicki Levi** (LEVI) or **Sandra Valencia Gonzales** (VALENCIAS).

Charlene Cherry is Chief, Management Analysis Branch, Division of Planning, Evaluation and Resource Management.