news along the pike

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CENTER FOR DRUG EVALUATION AND RESEARCH

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INSIDE . . .

PIKE'S CORNERS . . .

Future of drug regulation in CDER's Hands

Center Director Reviews Current Status, Issues, Challenges

BY JANET WOODCOCK, M.D.

The people of CDER must choose their role in shaping the future of drug regulation. We have a choice of being dragged along by the forces of change or taking charge of our public health mission and leading. The lack of consensus on many important issues at the recent stakeholders' meetings (August *Pike;* this issue, page 9) means that people are looking to the Center and the FDA for leadership. In particular, consumers, who in many cases lack scientific sophistication, trust the people at the FDA to do the right thing.

The current system of drug regulation has been in evolution over most of the 20th century. From its very inception, drug regulation has been pulled and pushed by various interests, each with its own point of view and advocacy group. These include physicians, pharmacists, members of academia, free market advocates, patient groups, consumer advocates, social reformers and those who benefit from health fraud. Historically, this has been a system besieged by change. The forces now driving change include: the end of the expansionist era of continuously rising Federal budgets; the advance of science and the acceleration of drug discovery; the rise of patient and consumer advocacy; and the globalization of the pharmaceutical industry.

Status of CDER

Currently, we are in good shape, well-regarded and considered a powerful organization. We have a robust premarket review program. Our large inspection program, operated in conjunction with the field, ensures good quality for U.S.-marketed drugs. One of our historical areas of regulation, drug advertising and promotion, continues to be controversial. We face challenges in compliance and enforcement issues.

Premarket approval: In new drug reviews, we have an award-winning program. Our challenge is to implement PDUFA 2 and meet all its requirements. In addition, clinical guidances must be updated, and our four years of work on good review practices need to be brought to fruition. Our generic program is highly productive and efficient. We are working very hard and using science-based standards for approval. While the central challenge in generics is a scientific one, we face an issue in evaluating obstacles to generic competition.

Our over-the-counter drug process is in good shape now that issues about who manages OTC drugs have been resolved. The monograph process is on track.

Post-marketing surveillance: We are not meeting statutory deadlines for post-marketing

(Continued on page 10)

Malinowski Selected as Mansfield Fellow

Scientist to Spend Year with Japanese Drug Regulators

Henry Malinowski, Ph.D., begins an unusual sabbatical at the end of the month—a year of Japanese language and area studies, followed by a year working with Japan's drug regulators. Dr. Malinowski, the first FDA employee selected as a Mike Mansfield fellow, will join five other Federal officials in the two-year program.

Dr. Malinowski, Director of the Division of Pharmaceutical Evaluation I, Office of Clinical Pharmacology and Biopharmaceutics, first became interested in Japan during a Far East trip to Expo '90 in Osaka. Since then, he and his family have made several other trips to Asia. He applied for the fellowship after reading a one-line announcement last year in Mike Causey's Washington *Post* column.

"It's one of those things that the more I found out about it, the more comfortable I became with the idea. I always wanted to learn Japanese." He has worked with Japanese experts who have spent time with the Center learning about U.S. systems. He has stayed in

(Continued on page 9)

JOE'S NOTEBOOK

A New Look—Easier to Read, PDF Hints

I hope you find the *Pike's* revised layout easier to read, whether it's a photocopy you're holding in your hands or the on-line version you have up on your computer screen. It's been two years since I took over editing the *Pike*, and some of the *Pike's* fans have noted a facelift has been in order for some time. Special thanks to **John Senior, M.D.,** and one of OTCOM's summer interns, **Jason Walther,** for urging me to take a long, hard look at the Pike's design.

According to the design gurus, the new, shorter, justified columns are the optimum length for ease of reading—with the exception of this column. Each page now has more "color," eye candy if you will, even though it's still basically black and white with some blue in the on-line version.

It wasn't easy getting to this point, however. As many of you are painfully aware, fiddling with a computer program's default settings is similar to pulling out the bottom card from a house of cards. A small change you thought simple turns out to be like a pebble you tossed into a quiet lagoon, sending ripples into all the nooks and crannies of the shoreline.

So, I thought I'd pass along three hard-won lessons from this exercise that any of you creating PDF files might find useful:

- If you're using Microsoft products, like most of us, and their TrueType fonts, stick to Times New Roman and Arial. Adobe substitutes either Helvetica or Times for any TrueType fonts you've chosen. Arial and Times New Roman are a close match, and the substitution usually goes undetected. It's true, you can embed TrueType fonts when you create PDF files. Unfortunately, your fonts will be bit-mapped and have jagged edges rather than the smooth edges you had in the Microsoft program. Plus, your PDF file will grow to immense proportions, be slow to load and difficult to read on-line.
- Once you leave default settings behind, avoid letting the program set anything automatically. Pick the exact spacing for paragraphs and lines that you want. This may help keep your publication from reformatting.
- If your publication still reformats, you have two choices. A fail-safe method is to pick the PDF Writer or Distiller as your printer and only print from the Acrobat Reader or Exchange. Second, if you can configure your office printer as a PostScript printer, the printouts from your program and the PDF version may still look the same—and that's a big "may."

Let me know of other changes that you'd like to see. If you're interested in joining the Editorial Board, e-mail me at OLIVERN. We have had a couple of departures in the past months, and fresh viewpoints are always welcome.

MEDWATCH: You can now report adverse events and product problems directly to MedWatch on the Internet. You can find a link to the voluntary reporting form by going to the MedWatch homepage (http://www.fda.gov/medwatch), clicking on How to Report, then Reporting by Health Professionals or Reporting by Consumers. The direct address is https://www.accessdata.fda.gov/medwatch/medwatch-online.htm (the "s" is required after "http" to access the secure server).

CORRECTION: Office of Compliance's **Peg Tart** reports an error in the paragraph about the Compliance Coordinating Committee on page 9 of the August *Pike*. The first sentence should read: "The CCC facilitates communication between the Office of Compliance and other CDER units." The on-line version was fixed; but, if you've filed one of the original photocopies, you may wish to make the change or download the corrected version.

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

Better Internal Meeting Management—Just a MAPP Away

BY JIM MORRISON

Whenever industry representatives talk about how CDER has improved over the past few years, meetings are usually mentioned. We are perceived as scheduling meetings in a more timely manner and running the meetings more effectively. Those of us who regularly attend internal CDER and FDA meetings would probably not find the same improvement in that arena.

Whether we work in the new drug review or other areas of CDER, we are under constant pressure to work more efficiently and effectively. While we have streamlined many of our processes, we will need to reduce the expenditure of resources even more. Where is the fat now? There is a fair chunk of it in internal meetings.

Wasting time in meetings is not a CDER invention. It seems to be universal. In a recent private sector survey, 80 percent of managers estimated that half their time spent in meetings was wasted. I would guess that a survey of CDER managers would yield about the same results. The biggest gripe I hear about internal meetings is that we often have the same meeting over and over again, because the first meeting failed to arrive at a clear decision or consensus.

The question, then, is: "Why can't we improve the effectiveness of internal meetings the same way we improved external meetings?" The answer is: "We can!" Why don't we then, and since everyone has the same problem, why hasn't it been successfully addressed in so many organizations?

I put the question to **Bob Potter,** an expert in meeting management who teaches a course on effective meeting management for the Parklawn Training Center. He believes that most managers do not think of meeting time as a resource to be managed. However, most supervisors and managers average about 35 percent of their time in meetings. If half that time is wasted, it represents more than a sixth of the salaries of CDER management. That is a substantial amount of money, not to mention the lost opportunity for doing other work while half the meeting time was being wasted.

Effective meeting management is not rocket science. That's unfortunate, since if it were, perhaps we would devote more time and attention to it. The basics for effective meetings are contained in the external meetings MAPP (4512.1) and other sources:

- Having clearly stated objectives for the meeting.
- Having the right people present and adequately prepared to discuss the issue.
- Keeping to a written agenda with realistic time allotment.
- Taking good minutes that record decisions made and that are circulated promptly to everyone in attendance.
- Assigning action items with due dates that are tracked and followed up.

For those who are new to running meetings or others who feel a little rusty on the subject, there are courses available from CDER's Division of Training and Development (contact **Janice Newcomb**, 7-1262, NEWCOMBJ) and from the Parklawn Training Center (3-6790). In addition, **Beverly Compton** of PTC highly recommends a book, *How to Make Meetings Work: The Interaction Method*, which is available at the PTC office in Parklawn, Room 16A-55. For managers who would like their staffs to get training *en masse*, both training offices are glad to bring training on site.

Jim Morrison is the Center Ombudsman.

Karl Flora Mourned, International Authority on Pharmaceutical Chemistry

BY CHARLES K. GREISHABER, PH.D.

Karl P. Flora, Ph.D., Director of the Division of Product Quality Research, died Aug. 31, as a consequence of non-Hodgkin lymphoma. Dr. Flora, a resident of Centreville, Va., is survived by his devoted wife, the former Patricia Webb, and two beloved sons, Kyle, a junior at Bridgewater College and Kevin, a senior at Centreville High School.

He also leaves behind his loving parents, Kermit and Pauline Flora of Bridgewater, Va., a brother, Ronald of Randleman, N.C., and many friends and colleagues who are universally indebted to him for his kindness and gentle guidance.

Dr. Flora received his bachelor's degree in chemistry from Bridgewater College and a Ph.D. in pharmaceutical chemistry in 1976 from the Medical College of Virginia. He then undertook a research associate appointment in the Department of Pharmacy and Pharmaceutics at the same institution.

Dr. Flora, who was born in Connellsville, Pa., came from Richmond to the Washington area in 1977 as a research scientist at the National Cancer Institute. There he spent 16 years in the Pharmaceutical Resources Branch in several capacities including branch chief. One of his more cherished activities was serving as coordinator of pharmaceutical and chemical development of anti-AIDS drugs from 1987 to 1990.

In 1993, he joined the FDA as director of pharmaceutical chemistry research. His research interest continued in dosage form development and analytical chemistry, especially for anti-cancer agents. He is distinguished for cultivating the development of a Product Quality Research Initiative fostering research interactions between CDER and industry on enhancing pharmaceutical quality.

Throughout his professional life Dr. Flora was an internationally recognized authority in the pharmaceutical chemistry of anti-cancer drugs. In addition to his active research and administrative duties at the Center, he served as chairman of an international committee dealing with worldwide issues of dosage form development for new anti-cancer agents.

Dr. Flora was a member of numerous honorary, professional and scientific societies, including a charter membership in the American Association of Pharmaceutical Scientists. In private life, Dr. Flora was an attentive husband, a fervent father, an ardent alumnus of Bridgewater College and an active member of the Manassas Church of the Brethren.

INFORMATION TECHNOLOGY CORNER

OIT Seeks Comments on New MAPP to Triage IT Service Requests

BY VALI TSCHIRGI

The Office of Information Technology is proposing a MAPP to streamline procedures for handling requests for OIT services. The MAPP and new procedures are being distributed for comment throughout the Center.

CDER's increasing use of computer technology means OIT receives a growing number of service requests that range from requests for help with operational failures to requests to develop new ORACLE database applications. In order to provide the highest level of customer service, enable improved planning, improve accountability and foster communication, a more systematic and standardized approach was needed.

OIT organized a working group to discuss past problems and recommend a solution. The result is a new method of formally triaging and managing requests. The following levels of service are defined:

- *Operational:* time-critical services in support of an operational failure such as a network outage, a problem running a network database application, e-mail problems and virus reports.
- *Level I:* routine services, which require relatively few OIT resources and can be completed fairly quickly, such as installation of a new PC, creation of a network shared area and access to a database application.
- *Level II:* non-routine services, which require greater OIT resources, must be coordinated between OIT and the user's staff and generally take more time to complete. Examples are the development of a new ORACLE database or the modification of database application software.

Procedures for both the service requester and OIT have been defined for each of the levels above. Once the MAPP is in final form, OIT expects all requests to come through the Help Desk and follow the procedures specified in the MAPP and *OIT Services Manual.*

The *OIT Services Manual* contains the detailed procedures for submitting Level I and Level II service requests. The manual is available in the following three locations:

- OIT intranet page (http://oitweb/oit.).
- X:drive at \oitsrvman\ser-man.pdf.
- Help Desk.

No changes are being made to procedures for reporting operational problems to the Help Desk. If you have an operational failure, please report it to the Help Desk as soon as it occurs. Operational problems are time critical and will receive immediate attention.

The Help Desk phone number is 7-0911. The e-mail address is HELP or HELPDESK.

If you have any questions concerning the new procedures, the MAPP or the *OIT Services Manual,* please e-mail **Judy McIntyre** (MCINTYREJU).

Vali Tschirgi is a computer specialist in OIT's Division of Quality Assurance.

ADMINISTRATIVE MANAGEMENT CORNER

Budget, Procurement Subcommittee Seeks to Streamline Financial Plans

BY ANITA HARRELL

Budget and Procurement is one of the subcommittees of the Administrative Management Coordinating Committee. Our role is to streamline and provide continuous improvements to the budget process within CDER. The monthly meetings provide an opportunity for members to discuss both the best practices and the problems within their program areas.

Representatives from each of the superoffices serve on this subcommittee: OCD, **Carol Norwood,** executive secretary; OM, **Rixie Scott** and **Susan Persh;** OIT, **Alice Gray;** ORM, **Wayne Amchin, Barbara Durst, Tammy Russell, Barbara Shekitka, Kellie Wragg, Angie Davis, Zulema Miguele;** OPS, **Tina Hamilton;** OTCOM, **Heidi Burch;** and OC, **Anita Harrell,** chair.

Members are combining their budget and computer skills to design spreadsheets for use by the entire Administrative Management Team. **Barbara Shekitka, Barbara Durst** and **Kellie Wragg** had volunteered to design an Excel spreadsheet and brought it to the subcommittee for discussion. Modifications were suggested so that users could adapt it to individual offices or divisions. Further discussion identified the need for quarterly and year-to-date reports. The design team will incorporate a summary sheet which will automatically calculate the figures from the individual quarterly sheets.

One of the challenges for budget analysts, management and administrative officers, and management and program specialists is the preparation of the financial operating plan. Plans are formulated at the division level, which are then incorporated into an office plan. In the Offices of Review Management and Pharmaceutical Science, office plans are incorporated into superoffice plans.

The initial submission outlines the spending plan for the entire year. At the end of each quarter, the actual expenses are recorded, based on the Agency's Office of Financial Management accounting printout, and the projections for the remaining quarters are updated. Since most of the Center has both appropriated dollars and user-fee dollars, the financial operating plan is also divided into appropriated and user-fee dollars.

At the August subcommittee meeting, **Wayne Amchin** distributed copies of ORM's financial operating plan spreadsheet that he created. The spreadsheet contains formulas to split funding into appropriated and user-fee categories, and each office's plan is linked to the superoffice plan. September's meeting includes a final review of the revised budget report spreadsheet and a more in-depth explanation of the ORM's financial operating plan spreadsheet. The subcommittee's goal is to have these two spreadsheets available on the X:drive for use by the AMT early in fiscal year 1999.

Anita Harrell is a senior management officer in the Office of Compliance and chair of the AMCC Budget and Procurement Subcommittee.

REVIEWER'S CORNER

Window Opens for Intramural Research Grant Proposals

BY ROSE CUNNINGHAM

Center scientists have until Oct. 9 to submit research proposals for regulatory science and review enhancement projects. The Center anticipates that about $250,000 will be available for fiscal year 1999 to fund these intramural projects, with a limit of $50,000 for any individual project. Projects should ultimately facilitate the process of pharmaceutical development, the design and conduct of clinical trials, preparation of applications for investigational new drugs and new drugs, the submission and review of applications, post-marketing safety assessment and the regulatory use of such data in carrying out CDER's mission.

In addition, the Office of Women's Health will make a formal announcement on Oct. 1 for its fiscal year 1999 intramural research grants. Areas of mutual interest to OWH and CDER that have been identified as priorities are gender effects, drugs in pregnancy and pregnancy labeling; adverse events for fertility drugs; dietary supplements; and consumer education and outreach for hormone replacement therapy.

The one-page concept papers will be due by Oct. 23. The Center will evaluate and rank those concept papers and forward the top four or five to OWH for determination of the three to be developed into proposals to compete for the OWH funding. Deadline for submitting proposals for Office of Science grants has passed.

Regulatory science and review enhancement refers to any activity involving the exploration of approaches, methods or data that could potentially enhance the quality or efficiency of the drug review process or the design and evaluation of clinical or non-clinical protocols.

One largely untapped resource at CDER, for example, is the large collection of applications for approved drugs. While these data are not currently stored in a form that facilitates comparisons across drugs in a class or across classes, one goal for a project of this type might be to develop methods for creating databases that would permit such comparisons, both for effectiveness and for safety outcomes. Having access to such databases would facilitate the review of new drugs.

Other projects might also be facilitated by the availability of a usable NDA database, for example, the selection of appropriate efficacy outcomes for future studies, the establishment of variance data to use in sample size estimation for future studies and the development of analytical approaches for looking at both safety and efficacy data.

Other questions related to trial design might also be answered by exploring large databases from completed studies. A successful example of such an effort was an exploration of the relative risk of serious cardiovascular events in patients with stable angina assigned to either drug or placebo in 12 trials of anti-anginal drugs submitted in support of new drug applications (Glasser, S.P., and others, 1991, "Exposing patients with chronic, stable, exertional angina to placebo periods in drug trials," *JAMA*: volume 265, pages 1550-1554). This exploration revealed that placebo treatment did not increase the risk of such events in these patients and, thus, provided justification for FDA guidance recommending placebo controls in trials of this type.

Research proposals will be reviewed on the basis of improvement to the quality and efficiency of the review process, scientific merit, cost, probability of success and the knowledge, skills and experience of the investigators.

Signed proposals for both the CDER and OWH programs should be sent to me at the Executive Operations Staff, HFD-006, Room 6055, Woodmont II. For more information and application forms, call or e-mail (4-6779, CUNNINGHAMR).

Rose Cunningham is a regulatory health project manager.

Tony Langston Dies

Former CDER Employee

Thomas D. "Tony" Langston, one of the original employees of the Drug Listing Branch and later the Advisory Opinions Branch, which was the forerunner of the Drug Information Branch, died Sept. 16 after a courageous fight with leukemia.

Tony was a graduate of the Pharmacy School at Howard University and the 1995-1996 president of the District of Columbia Pharmaceutical Association.

He left CDER to become an international trade specialist with the Agency for International Development. Tony is survived by his wife of 39 years, Dianne, three daughters, a brother and sister, three granddaughters and numerous other relatives and friends.

COMMUNICATIONS CORNER

Choose the Right Color for Your Presentation

Keep these color choices in mind when you prepare visuals for a presentation:

- *Limit colors* to no more than three.
- *Stick to* the same color scheme throughout to code like elements.
- *Use warm* colors—red, orange or yellow—for items you wish to stress. Warm colors visually advance the elements on the screen.
- *Pick red* to call attention to main points, show priorities or signal danger or crisis points. Red generates energy and excitement. People are used to it as a warning sign.
- *Select green* to list things you want the audience to do or decisions you want them to approve. Green encourages people to think.
- *Use bright yellow* to highlight goals and objectives. Yellow signals optimism and confidence.
- *Switch to blue* when you need to calm an audience because it can lower blood pressure and pulse rate. However, too much blue can impair concentration.
- *Avoid large* amounts of purple because it disturbs the eye's focus.

Source: Isabel Kersen, Performance & Learning Associates, Secaucus, N.J., writing in Sales And Marketing Strategies & News, Hughes Communications Inc., 211 West State St., Rockville, Ill. 61101.

UNION CORNER

Spotlight Falls on Exclusive Representation, Collective Bargaining

BY ROBERT YOUNG

The Civil Service Reform Act includes two interrelated provisions, exclusive representation and collective bargaining, to assist in securing achievement of its stated goal: "the effective conduct of public business."

- Section 7111 states: "An agency shall accord exclusive recognition to a labor organization . . . selected as the representative . . . by a majority of the employees . . . who cast valid ballots . . . "
- Section 7114(a)(1) states: "A labor organization which has been accorded exclusive recognition is the exclusive representative of the employees . . . and is entitled to act for, and negotiate collective bargaining agreements covering all employees . . . "
- Finally, Section 7114(a)(4) provides: "Any agency and any exclusive representative . . . shall meet and negotiate in good faith for the purposes of arriving at a collective bargaining agreement."

Collective bargaining agreements are the *raison d'être* of unions. Although civil service employees have many rights granted by the Constitution and various statutes including the CSRA, the bargaining agreement—the contract—is the principal embodiment of their rights in the work place. Like any other contract it is a series of mutual promises which are proscriptive and legally enforceable and are appropriately contrasted to vain hopes, empty promises and gifts.

So long as the rules regulate and relate to personnel policies and practices that affect working conditions, there is no limit save exhaustion to the workplace matters that can be addressed and regulated in the contract. Standard subjects include compensation issues such as overtime, as well as time of work, place of work, performance appraisal, awards, discipline, details, promotions, assignment of work, assignment of offices, training, professional development, discrimination and occupational safety.

The statute in Section 7114(b)(1) requires that bargaining be in good faith, that the agency and the union must "approach the negotiations with a sincere resolve to reach a[n] . . . .agreement." Bargaining is termed collective because all employees in the bargaining unit are together represented and the contract binds all employees in the unit.

Exclusivity is the pragmatic statutory tool given to the majority representative to assist it in bargaining with the agency. Exclusivity, according to Section 7111, restricts the agency to dealing solely with the majority representative in personnel matters related to working conditions and the workplace. Exclusivity curtails the ability of an agency to weaken the employee majority by dividing it. Having only one spokesman, albeit a democratically chosen one, amplifies and focuses employee voices. The employees act in concert, in unison, in union. Partly by sheer mass they become a force that cannot be ignored. This is attainable by unorganized and uncoordinated individuals.

The National Treasury Employees Union was certified as the exclusive representative of all FDA bargaining unit employees nationwide. CDER employees are included in the FDA Headquarters, Washington, D.C., area chapter. Contract negotiations are scheduled to begin in September. FDA employees have suggested a wide range of issues to be addressed.

Robert Young, M.D., Ph.D., is interim president of Chapter 282, NTEU.

DRUG APPROVALS IN THE NEWS

Once-Daily Drug for HIV, AIDS Granted Accelerated Approval

Efavirenz, a new drug to treat HIV and AIDS in children and adults, was granted an accelerated approval on Sept. 17. CDER received the application on June 11. Efavirenz, in combination with other anti-retroviral agents, was approved to treat HIV-1 infection after 24-week studies showed it effective in suppressing HIV. The effect on viral suppression beyond 24 weeks has not been demonstrated. The treatment is taken once a day, which can be beneficial to people who must take several drugs concurrently.

Efavirenz is the third non-nucleoside, reverse transcriptase inhibitor approved. The results of three adequate and well-controlled trials conducted in 928 adults and an uncontrolled open-label study conducted in 57 pediatric patients (some as young as age 3) support the safety and efficacy of efavirenz. Additional supportive information on safety and activity is provided by the results of Phase I and Phase II trials and the sponsor's expanded access program.

Drug labeling recommends that patients take 600 mg of efavirenz once daily in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors. Although the drug may be taken with or without food, as desired, the label suggests that patients avoid high-fat meals. Health care providers should consult the drug labeling for a discussion of drug interactions with efavirenz.

Nervous system symptoms, such as dizziness, insomnia, impaired concentration, abnormal dreams, and drowsiness have been reported in more than half of patients treated with efavirenz. These symptoms generally occur in the first or second day of treatment and usually resolve as treatment continues. Additionally, bedtime dosing may make these symptoms more tolerable. Patients should avoid potentially hazardous tasks such as driving or operating machinery, if they experience these symptoms. Reports of delusions and severe acute depression have also occurred, predominantly in patients with a history of mental illness or substance abuse. Efavirenz should be discontinued in patients with these more severe symptoms.

During clinical trials, about 27 percent of patients treated with efavirenz experienced a skin rash, compared to 17 percent of patients in control groups. Severe rash, requiring stopping efavirenz, was infre-

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PROJECT MANAGEMENT CORNER

Sponsor Preparation Increases Meeting Productivity

A style of meeting management pioneered by the Division of Oncology Drug Products has been favorably received by sponsors, alleviated much of the burden of minute preparation. After a recent meeting involving a novel pivotal trial proposal, **Jean Yager**, the Center's director of project management, and **Dottie Pease,** supervisory project manager in the Division of Oncology Drug Products, received an enthusiastic report from Toni Marie Sutliff, the sponsor's consultant. Toni's observations highlight the importance of thorough sponsor preparation to highly productive meetings.

The initiative for meetings remains with the sponsor, who is responsible for submitting a written request for a meeting that, among other things, identifies the purpose of the meeting, lists the specific objectives or outcomes expected and proposes an agenda.

For this meeting the sponsor prepared a briefing package divided into sections for each of the review team's disciplines. Each section began with a short statement of the specific questions and the sponsor's proposed responses as an executive summary. The body of the section presented just the detail necessary for the reviewer to understand the context of the question and the rationale behind the sponsor's proposed responses.

Both the sponsor and the review team held pre-meetings. During the division's pre-meeting, review team members prepared overhead transparencies, one for each of the sponsor's questions with the division's proposed responses. The sponsor's team also held a pre-meeting to brainstorm possible issues that the reviewers might raise.

At the actual meeting, the sponsor was asked to forgo a formal opening presentation. After introductions, the Oncology Division displayed each of its overheads. The discussion was focused and lively. The participants were able to resolve 11 key issues in 90 minutes.

The division's minutes consist of the overheads with any agreed-upon changes. The division was able to deliver photocopies of these to the sponsor at the end of the meeting.

Toni reported these lessons learned:

- Organizing the briefing package into sections by review discipline makes the review team's job easier.
- Adding an overview of the questions to the introductory section of the briefing document would have made it even more useful.
- Avoiding the opening presentation worked to the sponsor's advantage by allowing more time for meaningful discussion.
- Being open with the proposed trial design and asking difficult questions—the answers to which the sponsor wasn't sure it wanted to hear—led to a richer discussion.
- Asking difficult questions and providing full information enabled the review team to do appropriate research and provided detailed responses and recommendations.

Both the review team and the sponsor benefited from the sponsor's preparation for this meeting. Both parties were able to reach agreement on a novel pivotal trial design.

Tony is a consultant working for McCulley/Cuppan LLC in Salt Lake City, Utah, and can be reached by phone at (801) 736-5100.

Dottie can be reached by e-mail or phone (PEASE, 42472).

CDER Approves 1st Oral Drug for Rheumatoid Arthritis

(Continued from page 6)

quently seen in clinical trials.

The labeling also recommends that health care providers monitor patients' liver enzymes, especially in those infected with hepatitis B or C viruses. Cholesterol levels should also be monitored because clinical studies were unable to distinguish whether this drug contributed to elevated levels. Several AIDS drugs have been associated with increased cholesterol and liver enzyme levels. Adverse reactions in pediatric patients have been similar to those seen in adults, with a higher incidence of and more severe rash than in adults.

Information from some preclinical studies showed that efavirenz appears to cause birth defects, so women should be screened for pregnancy before starting treatment and should be encouraged to use effective contraception. The sponsor has established a pregnancy registry to track fetal exposures. DuPont Pharmaceuticals of Wilmington, Del., manufacturers efavirenz under the trade name Sustiva.

The Center on Sept. 10 approved leflunomide, the first oral treatment for active rheumatoid arthritis. The drug was approved for slowing progression of this painful and disabling chronic disease. Although the drug does not cure rheumatoid arthritis, it has been shown in clinical trials to provide relief for painful, swollen joints caused by the disease and to retard damage to joints.

Leflunomide's ability to retard the progression of rheumatoid arthritis and to provide relief from the symptoms of this disease was shown in three controlled clinical trials involving more than 1,700 patients of whom 800 received leflunomide. X-rays of hands, wrist and feet were used to assess effectiveness in reducing structural damage to joints.

Because animal studies raised concerns that the drug can cause birth defects, a special warning included in the labeling states that leflunomide should never be used by pregnant women or women of childbearing age who are not using reliable contraception. Because the drug persists in the body for a long time, a drug elimination procedure is recommended for patients who want to become pregnant after taking leflunomide.

Adverse effects include risk of liver toxicity, diarrhea, hair loss and rash. Liver enzymes of patients taking leflunomide should be monitored, and the drug is not recommended in patients with significant liver disease. The new drug will be marketed by Hoechst Marion Roussel of Kansas City, Mo., under the brand name Arava.

Source: FDA Talk Papers.

REVIEWER AFFAIRS CORNER

RAC Meets with Senior Management Team

BY MELISSA MAUST

One way that the Reviewer Affairs Committee lives up to its mission of providing a forum for primary reviewers, improving communication among reviewers and representing the needs and concerns of primary reviewers directly to the Office of the Center Director is the quarterly meeting between the RAC and the Senior Management Team. The RAC met last month with the SMT to present an update of RAC activities and to discuss any new issues of interest to reviewers and management.

The Quality of Worklife Subcommittee report was given by **Terri Rumble.** She informed the SMT that the focus of this subcommittee, newly formed in 1998 (August *Pike),* was to identify a purpose, goals and objectives. The purpose of the subcommittee is to identify issues that affect the quality of our daily worklife and work toward providing a more supportive and satisfying work environment. The goal is to create an environment that ensures partnership and respect for all members of the CDER community. One of the issues that the group will focus on is how to maximize communication and accountability to the CDER community about priorities, including equality of benefits and opportunities across divisions and teams.

The subcommittee plans to prepare a white paper to be submitted to the RAC for comment. Center Director **Janet Woodcock, M.D.,** noted there was continued interest at the HHS and Agency levels in improved quality of worklife and that new initiatives are expected in the near future. **Paula Bourkland** said that the Agency's Quality of Worklife Committee has solicited ideas from the centers, and she volunteered to be the liaison between CDER groups and the Agency. This subcommittee will provide Paula with the information she would need to relay issues and ideas to the Agency.

The Networking Subcommittee has found a new chairperson, **Lydia Kieffer.** She is planning a meeting to discuss the preparation of a Reviewer get-together event to be held before the end of the year. Dr. Woodcock noted the lack of interaction between reviewers in different organizations was a familiar complaint and expressed her support for this effort.

The Team Model Task Force report was given by the chairperson, **Raj Uppoor.** The group finalized and compiled comments on the "Proposal for the Enhancement of Multi-Disciplinary Team Approach to Review of Submissions" dated Jan. 26 (March *Pike).* The comments were sent to **Jean Yager** on May 20. The group is hoping for a meeting in the near future to develop a strategy for continued work on this document.

The RAC is hoping to form a working group in cooperation with Ms. Yager that will include representation from all disciplines. In the process of reviewing and commenting on this document, the RAC has found out that there are many approaches to team review that are being practiced throughout the Center, and the RAC is hoping to identify and mark the best practices. Dr. Woodcock is supporting the team approach to reviews and the construction of such a document to explain the roles of the team members.

The Comparable Pay Subcommittee report was given by chairperson, **Milton Sloan.** He noted that **Ellen Johnsey** and **Karen Keonick** from the Office of Management had recently joined the group. The subcommittee is looking for issues to address and several were presented by the SMT, such as pay for statisticians.

Dr. Woodcock indicated her interest in learning how reviewers are functioning with all the changes that have taken place over the past years with respect to new guidances, such as those for the International Conference on Harmonization and the new one on "Submission of Abbreviated Reports and Synopses in Support of Marketing Applications."

Murray Lumpkin, M.D., Deputy Center Director (Review Management), expressed his interest in feedback on how the staff feels about the current process of developing, implementing and educating staff on changes. **Roger Williams, M.D.,** Deputy Center Director (Pharmaceutical Science) suggested a list of FDAMA implementation tasks and leads that might be helpful to staff and provided a copy to the RAC, which will be distributed at the next RAC meeting. If you are interested in a copy, please see your RAC representative.

In response to the Senior Management Team's interests about reviewers' views, the RAC will develop a task force to prepare a small survey for reviewers regarding the impact of implementing guidances and regulatory changes. The next quarterly meeting with the Senior Management Team will be at the end of the year.

For more details, the meeting minutes are located in the folder x:\coorcomm-\rac\qrtmtgs\.

Melissa Maust is a chemist in the Office of Generic Drugs.

Healthy People 2010 —Draft Objectives Released for 3-Month Comment

Urging Americans to help develop national health objectives for the coming decade, HHS Secretary **Donna E. Shalala** on Sept. 15 released *Healthy People 2010 Objectives: Draft for Public Comment*, which proposes more than 500 national objectives for improving the health of Americans by the year 2010.

"The Healthy People initiative has defined the nation's health agenda for the last two decades. It identifies the most significant opportunities to improve health and focuses public and private sector efforts on those areas," Shalala said.

"At a time when consumers are expressing an unprecedented interest in decisions related to their health, our call for citizen involvement is especially fitting."

The public comment period ends on Dec. 15. A Healthy People 2010 Web site enables the public to view and comment on the document electronically at http://web.health.gov/healthypeople. Healthy People 2010 has two overarching goals: to increase the quality of years of healthy life and to eliminate health disparities.

Malinowski to Spend Year Learning Japanese Before Year in Japan

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contact with Nobuo Aoyagi who came to the Agency 10 years ago on a one-year grant from the Japanese government and is now in biopharmaceutics. A little over a year ago, Japan published a bioequivalence guidance, and the Center evaluated the English language version.

Dr. Malinowski is interested in studying Japan's drug approval process, drugs approved in Japan and drug dosing in order to become a resource to the FDA on Japanese drug information topics. Dr. Malinowski received his bachelor's, master's and doctorate degrees from the Philadelphia College of Pharmacy and Science. His career has been focused on biopharmaceutics—how drugs are formulated, their dosage forms, dissolution testing and how they are absorbed. He has been with the Agency for 22 years.

Dr. Malinowski said he faces a real challenge in learning the Kanji characters that are used for many technical terms in Japanese. The language barrier has been so great in the past that it has stood in the way of American understanding of the Japanese system. Drug applications in Japan, for example, are submitted in Japanese, unlike the European Union that uses English as a standard.

While the most commonly used drugs in the United States and Europe are very similar, those used in Japan are different. Dr. Malinowski said that he is very interested in exploring these differences, not only in actual drugs but in how they are developed. He suspects that the Japanese system may place more emphasis on safety and the development of lower doses, while the U.S. system emphasizes effectiveness and that results in higher doses.

Support within the Center and the Agency for his two-year effort has been "tremendous," Dr. Malinowski said. He will be maintaining his current e-mail address during his two-year detail. One of his projects is to establish two-way contacts between FDA drug regulators and their counterparts in Japan. He envisions establishing contact through the CDER intranet. Those interested in his project can contact him by e-mail (MALINOWSKI). He has promised regular reports to *News Along the Pike* about his adventures.

The Mansfield fellowships, established and funded by Congress in 1994, are building a core group of U.S. government officials who can be a resource to their agencies on Japanese issues because they understand the political, economic and strategic dimensions of the complex U.S.-Japan relationship. The intensive two-year program, administered by the Mansfield Center for Pacific Affairs, enables a select group of Federal employees to develop an in-depth understanding of Japan and its government through hands-on practical work inside Japanese government ministries and agencies. Dr. Malinowski will officially be on detail to the U.S. Information Agency while in Japan.

The Mansfield Center for Pacific Affairs directs the public policy and international outreach functions of the Montana-based Maureen and Mike Mansfield Foundation. Founded in 1983, the Foundation builds on Ambassador Mansfield's lifelong efforts to bring about improved relations and greater understanding between the United States and Asia.

Consensus Elusive at Office of Health Affairs, FDA Stakeholders' Meetings

Many of the themes presented at CDER's stakeholders meeting Aug. 14 were reprised for similar meetings held by the Office of Health Affairs and FDA on Sept. 8 and Sept. 14 respectively.

There was a consensus that the Agency should view its specific statutory obligations as its priority and limit its participation in new activities, especially those activities that are not within the scope of its core statutory requirements.

There was a difference of opinion among stakeholders about whether or not consumer education and information were a priority for FDA. This difference was expressed in terms of FDA's role in providing consumer education as well as the value of consumer education in improving health outcomes.

While there were some stakeholder groups who believed that FDA had no role in consumer education and information, other groups saw the FDA's role as essential in providing consumers with access to objective information and in leading to improved patient interaction with physicians and thus better treatments.

Making trade-offs in the context of constrained resources was difficult, and few recommendations emerged. In general, stakeholders believe that adequate resources should be appropriated, that FDA should continue to reengineer its systems and that the Agency should access the expertise of other organizations to meet its goals.

For example, third party arrangements were seen as valuable in such areas as research, standard-setting and some aspects of product reviews, for example, the review of efficacy supplements.

Making new, safe and effective treatments available to patients in a timely way is a high priority for FDA and stakeholder groups. In order to bring the premarket review and approval system to its optimal performance level, stakeholders recommended that FDA continue to strive for efficiencies, conserve resources and limit new activities that may compete with or interfere with the Agency carrying out this obligation.

Public participation and collaboration were recurring themes in the stakeholder presentations. Many groups called for the FDA to make its processes and procedures for public participation more effective, particularly those processes involving public meetings and advisory committees

Consumer and patient stakeholders emphasized that public participation processes should be open, transparent and receptive to outside views; that better qualified and disease-specific consumer representatives should be involved on advisory committees; and that FDA should allocate sufficient resources and provide needed training to support its public participation commitment.

More information is at http://www.fda.gov/oc/fdama/comm/default.htm

American People Look to CDER for Leadership in Drug Regulation

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inspections in the United States. Reaching consensus on a mutual recognition agreement with Europe on good manufacturing practice inspections would be a step forward, if it can be achieved.

Our surveillance of adverse reactions to medicines is in reasonable shape. We are forming the new Office of Postmarketing Drug Risk Assessment and reorganizing functions. The Adverse Event Reporting System will computerize the passive reporting system and provide for 100 percent electronic input and analysis.

Drug advertising regulations: This is a very active program. Our draft reprint guidance is already drawing fire. Direct-to-consumer advertising, especially on TV, is controversial. We will be evaluating the private, voluntary effort for quantity and quality of patient information sheets.

Compliance and enforcement: FDA has published a proposal on structure/function claims for dietary supplements. This is a controversial area where forces pull in opposite directions. There is much health fraud in the United States, but we don't put a lot of resources into this area unless there is a danger to the public health

Supporting activities. We have to do research. Our laboratory research has been cut, but is very robust. Our regulatory science research intramural grant program was very productive (page 9). We have a well-oiled machine in place for policy development. We're doing extremely well in the International Conference for Harmonization of Technical Requirements for Human Drugs.

Communications: We're putting out information and answering thousands of calls and Freedom of Information requests. CDER's Ombudsman is getting hundreds of calls for dispute resolution. We still have a backlog of citizens' petitions but are working hard to get them under control. Our Medical Library and training programs provide essential support.

Information technology: We're in very good shape thanks to PDUFA money. We hope to publish the guidance on electronic submissions this fall.

CDER's Future

We do not have the resources to accomplish all the tasks before us. Congress has invited us to involve our stakeholders and provide a priority-setting plan for statutory compliance.

Also, to help answer the questions of what we should do and how we should do it, the CDER Stretch Planning Group made a major effort, talked to various groups and came up with three recommendations:

- Focus on our public health mission.
- Tap the potential of every person.
- Build a powerful organization.

Public Health mission of CDER: Our stated mission is to promote and protect the public health by assuring that safe and effective drugs are available to Americans. This mission is too limited. It doesn't look at the outcome of medicine use. Our responsibilities don't stop at making drugs available: We need to make sure they result in better health.

Our goal is that drug regulation have the most positive public health impact it can. We sometimes focus on meeting goals and deadlines, but we need to keep the higher bar in front of us. At the end of the day, the public health must be better.

We have to continually evaluate priorities in terms of impact on public health. Here are some examples of current high impact areas for public health:

- Pregnancy labeling. For years we tolerated pregnancy labeling that doesn't adequately inform physicians and patients. Information must be relayed to pregnant women and their doctors in the most informative way.
- Antibiotic resistance. We need to get a grip on this emerging issue.
- Medication errors. These are often a preventable cause of death. This is an issue that needs resources.
- Information for consumers. They want unbiased information from us in language they can understand. We are going to have to sort out our direct-to-consumer advertising policy.
- Drug safety. Adverse reactions to medicines rank in the top 10 causes of death. This is a huge problem in the United States and one in which we need to take a leadership role. We should do more in education, better labels and more scientific research.

Tapping the potential of every person in CDER: The Stretch Planning Group has four parameters:

- Service. We choose to work in CDER because we make a difference. Management exists to allow you to do the best job you can.
- Inclusion. We can't regulate drugs well unless we include all points of view. When we include the patients, they become advocates for the drug regulatory system, not opponents.
- Meaning. We need to be engaged in work that adds value to the public health. We need to stop or diminish work that doesn't add value.
- Growth. We all need to grow as individuals and as an organization.

Building a powerful organization: We need to widen our scope of responsibility to include the public health impact of drug regulation. We need an organization of sufficient power to cope with that. There are no other bodies to exercise the leadership. Key tools for building a powerful organization include:

- Science: We need to incorporate current and future science.
- Computers. These are powerful tools to increase efficiency and productivity.
- Communications. This is one of our key activities and one that will help ensure the safety of drugs. We need to do more to communicate what we know about approved drugs.
- Management: We have to continue good management; chaos is not a platform on which to build.

Finally, the future of drug regulation will see a de-emphasis on the review phase as we move to continuous management of the drug life cycle. We need to understand communication science better and how it can change people's behaviors. Drug regulation will increasingly become an international activity, and a worldwide drug regulatory system will emerge.

Editor's Note: Dr. Woodcock's article is based on her Sept. 9 presentation at the CDER Scientific Seminar. Videotapes of her talk are available at the Medical Library and its branches.