news along the pike

March 1997

Center for Drug Evaluation and Research

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Inside . . .

Pike's Corners . . .

Ozone-Depleting Propellant Phaseout Proposed

Public Input, Patient Acceptance Targeted

The FDA published an advance notice of proposed rulemaking (ANPRM) March 6, which seeks public comment on a proposed strategy for the transition from chlorofluorocarbon (CFC) propelled drug products to non-CFC alternatives as these alternatives become available over the next several years.

The phaseout of CFC-based products is mandated under the U.S. Clean Air Act, EPA regulations and the Montreal Protocol on Substances that Deplete the Ozone Layer. The Montreal Protocol is an international treaty signed by over 150 countries, including the United States, which seeks to eliminate all use of ozone depleting substances, including CFCs.

Because of their role in damaging the earth's protective stratospheric ozone layer, the use of CFC propellants in drug products has been banned under FDA regulations since 1978, unless the product is deemed by the Agency to be an essential use of CFCs. The essential uses for drug products are listed in the *Code of Federal Regulations* and such uses are exempt from the general ban on the use of CFCs. These products mostly consist of metered-dose-inhalers (MDIs) for the treatment of asthma and chronic obstructive pulmonary disease. Based on the accumulating scientific evidence of depletion of the ozone layer by CFCs and other substances, and given the Montreal Protocol's planned eventual elimination of CFCs even from medical

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Rubber Hits Road at ICH Industry Training

By Norman Oliver

During a day-long training session last month, CDER scientists introduced quality guidelines developed from the International Conference on Harmonization (ICH) to nearly 350 experts in the drug industry. The training session, covering the stability of drugs, their impurities and the validation of methods used to test both, was sponsored by CDER's Office of Pharmaceutical Science (OPS). The training on seven ICH guidances that are being adopted took place at the University of Maryland's conference center in College Park and drew drug company representatives from across the country.

The Center members on the training committee were **Mike Olson, James Dunnie, John E. Simmons, Mike Theodorakis** and **Peggy Cunningham.** Drug companies and trade associations had 14 members on an industry training committee. The training was conducted under a collaborative agreement between CDER and the University of Maryland. University participants were **Gary Hollenbeck,** associate professor of pharmaceutical science, and education coordinator **Judy McGlone Dalby.**

ICH, officially known as the *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* brings together government regulators and drug industry experts from Europe, Japan and the United States. The ICH recommends ways to find consistency in product registration in order to reduce or eliminate the need for companies to duplicate testing during research and development of new drugs.

In the keynote address, Center Director **Janet Woodcock, M.D.,** outlined the "forces for change" driving harmonization forward:

- Globalization of industry. Ingredients are made in bulk and shipped all over the world for finishing. The FDA can no longer look just at the United States as a source of these products.
- Constrained resources. Regulatory agencies in other countries, not just the United States, face constrained resources for the

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Joe's Notebook

Harmonizing with Adam Smith

Every so often in these pages you read a summary from some meeting or other that I attended and found worth sharing. What's rarely captured in a report is the small talk that goes on in the hallways or while sharing a meal. Two snippets from recent meetings have stayed with me, not the least perhaps, because the other party couldn't fail to notice Food and Drug Administration on my name tag and thought I might pass his observations along—and so I will.

The first occurred in December at a consensus building conference on emergency stroke therapy. During one break, my low-fat diet was fighting a losing battle against the enticements of the hotel's chef. As I was trying to savor the broccoli and cauliflower and avoid the miniature crab cakes, a young doctor from overseas bent my ear. He was in this country, it turns out, on a research fellowship with a local medical school.

"What we need in my country," he said, pausing to spear a meatball with a toothpick and hold it enthusiastically before his mouth, "is an independent FDA." He munched with relish, speared another, and continued. "When I go out to eat in my country, I can't be sure of what I am putting into my body." I mentioned that even before I came to work for the FDA I was grateful for the Food Label that helped me with my diet.

Quite naturally, I explained how the FDA's conflict of interest and ethical standards provide an even-handed administration of rules. I added, then, that I worked for the Drug portion of the FDA. Since he was a physician, I was curious about the supply and quality of drugs he had available to care for people who are sick. When he could get medicine, he said, he couldn't be certain of its strength. He had to follow his patients closely, not simply write a prescription and send them off to the corner drugstore.

The second conversation took place at the Center's ICH training program. This time my conversational partner was a manufacturing quality control executive for one of those globe-spanning mega drug companies. "How important," I asked, "are these ICH activities to you and your company?" His aides-de-camp cocked their heads in attentive expectation of his reply. He thought for a moment, then delivered his answer with all the authority of a general who knows the strengths and weaknesses of his own forces, has a firm estimate of those of his foe, and has surveyed the ground between them. "This is," he pronounced, "the only way we can do business in the future."

Janet Woodcock observed in her opening remarks at the ICH training program that the birth of the process can be traced to a conversation among the regulators from several countries who were sharing a taxicab ride in Paris in the late 1980s. Adam Smith, it is generally believed, began work on his *Wealth of Nations* a decade before its 1776 publication during a trip to France.

While his observations on free trade have been recalled in public discourse lately, it is often forgotten that he also discussed the balance to be achieved between state regulation and private enterprise. In harmony they promote the public good. Either one alone and unfettered, however, leads to more harm than benefit. Indeed, Smith spent the last 15 years of his life as a public servant energetically "reinventing," "transforming" and "streamlining" the customs service of his native Scotland.

Smith's *Wealth of Nations* and our own *Declaration of Independence* share a common nativity year. One of the great stories of the last decade of the 20th century may turn out to be how a reinvented 18th century paradigm is transforming the way we work globally. The folks in CDER and their far-flung colleagues are writing the pages of that story every day.

news along the pike

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

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Ombudsman's Corner

Building a Career . . . Part Deux

By Jim Morrison

Last month, we discussed how leadership and other developmental programs can sometimes cure the "my career has fallen and it can't get up" syndrome! But there are other ways you can jump start a stalled career.

For most people, career growth doesn't just happen; it is the result of considerable planning and self-analysis. The key is to take control of your future, do some real soul-searching about what you want out of life and from your career (there are plenty of self-help books to guide you), and then develop a strategy for attaining your career goals with realistic milestones. You should reassess your goals and plans annually.

In the old days, career growth and progressive promotions through the managerial ranks were synonymous. Today, we live in a different world. Management is one career track, and it is still a rewarding one for those who have appropriate talents and skills. But don't automatically assume that management is for everyone.

I believe that there has never been a time in CDER when there were more opportunities to demonstrate leadership and to develop your career. The matrix management structure and the transformation effort in CDER have resulted in a proliferation of subject-matter coordinating committees, subcommittees, transformation results teams, and subgroups that are producing significant procedural and policy changes.

When the FDA Management Development Committee interviews candidates for the Leadership Development Program, we ask about the person's ideal job in the agency. From the answers we get, it is clear that many people have the mistaken impression that there is a group somewhere in FDA that sits around all day and makes all the policy. It is true that some organizational units have the word "policy" in their names, but policy is made throughout the agency and throughout CDER. If you see a need for a policy or procedure in your work, chances are there is a group working on it that would welcome your help. If there isn't such a group already, why don't you start one? Just discuss it with your supervisor first and with your colleagues, and you may find it is easier than you thought.

While the financial and recognition rewards structure has not kept pace with the reality that management and leadership are not necessarily vested in the same people, things are changing. For example, as her CDER Leadership Fellows project, **Nancy Smith,** Director of the Division of Biometrics III, has been doing some outstanding work in developing a non-supervisory career pathway for reviewers from new hire through what is called the master reviewer level.

If you want to take a look at the draft, go to the CDERnet (just type "Bambi" at the Internet address prompt, then click on Master Reviewer Program). I believe that the same type of management and technical dual career pathways will come to pass in the regulatory and administrative areas as well. Perhaps you can make it happen.

CDER has made great strides in improving communications, and you will see even greater progress in the future. If you need information about any of the CDER committees or who is on them, you will soon be able to find the information quickly. The CDER internal Web site, CDERnet, will become the central place for all information needed by center staff. The site was created only a few months ago, but is growing rapidly so keep watching it for the information you need in your career planning.

You can also get information through networking and mentoring. By developing contacts with people who have progressed along the routes you see yourself going, you can profit from lessons they have learned. CDER is developing a mentoring program for new hires, and it is in effect in some review areas. But even if you have been around CDER for a while, you can find opportunities to be mentored by more senior staff. Remember the rule for career building: Your career is your own; take responsibility for its growth and development.

Jim Morrison is the Center's Ombudsman.

Generics Launches Electronic Submission of Data

By Ted Sherwood

The Office of Generic Drugs has begun its program for electronic submission of bioequivalence data. The program was developed under contract with the University of Maryland. Under the program, drug companies may choose to prepare electronic submissions on diskette with the aid of a user-friendly software called "Entry and Validation Program." The program is free of charge to companies through the university's World Wide Web site (http://mundos.ifsm.umbc.edu/~fdacom). The Web site also permits companies to register as participants and to obtain updated information on the program, including any new versions. Companies can also ask technical questions through the Web site, which will be answered by university staff.

The program is expected to have a positive impact on the efficiency of reviews, ultimately reducing review times. In addition, the program will help reduce the time required to reach approvals. We strongly encourage firms to participate, and we hope to conduct training in conjunction with UM. The electronic submission program is part of a larger strategy for Electronic Regulatory Submission and Review, which will include the chemistry, manufacturing and controls portion of generic drug applications.

Ted Sherwood is a management analyst in OGD.

Administrative Management Corner

Committee Outlines Plans to Recognize Individual Efforts

By Charlene Cherry

The Administrative Management Coordinating Committee (AMCC) is working on a number of initiatives that will improve, enhance and streamline administrative processes in the Center.

For example, wouldn't it be nice as a new employee on your first day of work to be welcomed by a letter from the Center Director and an orientation package that tells you everything you really need to know about the Center. After many years of dedicated service to CDER, you would like to be appropriately recognized for the efforts you have put in over the years as an employee of the Center. This will be done with an exit letter from the Center Director. To go along with recognizing your efforts as you leave, supervisors will have at their fingertips a guide to help them determine and process appropriate career service and retirement awards. These are just some of the initiatives the human resources subcommittee is currently working on.

Other initiatives such as conducting seminars, training sessions and a two day go-away for administrative personnel are in the planning stages. The AMCC is also considering running focus group sessions with center administrative contacts and other Center employees to identify areas of concern that need attention. An on-line Administrative Handbook for use as a quick reference on administrative topics is also being developed for the CDERnet.

These are only a few of the things being looked at by the AMCC and its subcommittees. By way of this corner in the *Pike*, we hope to keep you updated on Committee progress, new initiatives and ideas. Membership on subcommittees of the AMCC is always needed. If you would like to become a member please contact the chair of the subcommittee listed below. Your comments and ideas are welcome. Please contact any member of the AMCC.

- Chair, **Paula Bourkland** (BOURKLAND), 594-6741, Chair, User Group.
- Executive Secretary, **Charlene Cherry** (CHERRYC), 827-0517.

Subcommittee Chairs

- **Tanya Abbott** (ABBOTTT), 594-6779, co-chair, Human Resources.
- **Tricia Desantis** (DESANTIS), 594-5465, co-chair, Human Resources.
- **Ruth Clements** (CLEMENTSR), 594-2420, Facilities.
- **Denise Rahmoeller Dorsie** (DORSIED), 594-5479, Information Technology for Administration.
- **Linda Brophy** (BROPHYL), 827-1651, Training.
- **Richard Vengazo** (VENGAZOR), 594-5476, Payroll.
- **Anita Harrell** (HARRELLA), 594-1058, Budget/Procurement.
- **Laurie Watson** (WATSONL), 3-0260, Travel.

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

EEO Corner

CDER Women Mark Decade of Progress, Advancement

By Diane Smith

This year marks the 10th anniversary for Women's History Month. This annual celebration was established in 1981 as Women's History Week, and in 1987, the observance was extended from one week to the entire month of March to commemorate the diverse contributions of women to this country.

The employment of women in the Federal government actually began during the Civil War. Whole sections of departments began to be staffed with women. Women worked in arsenals filling cartridge cases with powder, in the Treasury Department printing money, and in numerous agencies and departments working as copyists (the equivalent of modern-day typists). As a general rule, women in both government and industry did not receive titles, responsibility, or man-sized salaries until many years later.

In the early 1970s, women were employed far and wide in the Federal service. There was constant news of employment "firsts" for women as they entered into more jobs traditionally held by men. Soon the sight of women working as tugboat captains, heavy-duty equipment operators, traffic controllers, forest rangers, scientists, construction workers, doctors, managers, and supervisors would not be as startling as it seemed back then.

Closer to home, in 1987, when CDER had only 586 women, very few occupied policy-making positions, but things began to change in CDER after 1994. Today, we have 806 women, and they occupy many positions traditionally held by men. These occupations include, but are not limited to, center director, office director, deputy office director, division director, branch chief, and teamleader. As someone once said: "the old order changeth!" Although women have made considerable progress, more progress remains to be made.

Diane Smith is a member of the Center's EEO Staff.

Feigal Named Director at ODE IV

David Feigal, Jr., M.D., has accepted the position of ODE IV Office Director. Feigal had been serving in an acting capacity since the office was organized a little over one year ago. For the present, he will continue in his dual role of acting division director of the Anti-Infective Drug Products Division.

AMF Corner

Division Files System Development Well Underway

By David Isom

In the November issue of the *Pike*, we discussed how the Division Files System (DFS) pilot development effort would proceed using a new development tool. The new development tool, Documentum, was chosen after CDER determined that the original tool would not meet the Center's needs. The DFS is the cornerstone of the Administrative Management of Files (AMF) initiative. DFS provides document management, tracking, archiving, electronic signatures and search-and-retrieval capabilities for internally generated documents. It provides an electronic repository for final versions of review documents, letters, meeting minutes and records of telephone conversations.

The DFS development team is a joint effort led by the Office of Information Technology (interim) and includes team members from two contractors (SRA and Ioele Griggs) and the DFS working group.

After we switched to Documentum as our development tool, we spent most of October and November training the development team on Documentum, establishing our development environment and infrastructure, determining the scope of the DFS pilot and modifying our pilot system design based on the new tool.

DFS will be developed in phases. To develop a pilot quickly and help us focus on an area that would give the review divisions the highest payback, the first phase focuses on building the electronic document repository for final review documents and capturing the signature information. This phase will enable reviewers to check documents ready for signoff into the DFS, route documents for signatures, automatically archive the documents into the electronic repository and search the repository based on a variety of search criteria.

The DFS working group has been critical to the development of this phase. Since December, the working group has met every two weeks to evaluate demonstrations of different portions of the pilot system. Based on the comments we receive, we enhance the pilot and add additional capabilities before the next working group meeting.

We plan to deploy the DFS phase one pilot in the Oncology Division in May. Based on the feedback and success of the pilot, we plan to deploy phase one of the DFS in other divisions beginning this summer. As we deploy, the DFS working group will establish the priorities and requirements for subsequent phases of the DFS. Some high priorities already identified include full-text searching of documents in the repository and a feedback to COMIS mechanism.

David Isom is Acting Director of the Office of Information Technology (interim).

CDER Plans Parklawn Diversity Day Celebration April 8

By Gloria Marquez Sundaresan

On April 8, CDER is sponsoring the second Diversity Day Observance in Rooms D and E of the Parklawn Building. This event provides an opportunity for all hard-working government employees to reflect and take pride in their heritage and to learn more about different cultures.

It is a time to walk away from the pile on your desk to appreciate and celebrate the creativity and strength that diversity brings to the community. Diversity Day is an all-day event that begins at 9 a.m. There will be a variety of interesting things to see and do, such as:

- Exhibits from both private and public organizations.
- Cultural programs and presentations.
- Panels of speakers.
- A CDER EEO information sharing and training video: "The Ten Commandments of Communicating with People with Disabilities."
- A dance show, free lessons and a mini "ball."
- A fashion show.
- Food sampling ("The Taste").

Come in your traditional attire and get to know your coworkers. You can meet old friends and make new ones.

During the opening ceremony at 10 a.m., **CDR Tom Perez, CAPT Robert N. Burns** and the rest of the PHS Honor Guard will present the colors. Center Director **Janet Woodcock** will provide the opening remarks. Additional speakers include **Michael A. Friedman**, Lead Deputy Commissioner, and the Special Assistant to Sen. Barbara Mikulski, **Ms. Asuntha Chiang. Evelyn M. White,** Deputy Assistant Secretary for Human Resources, DHHS, will be the keynote speaker.

The Planning Committee needs to plan ahead for the Diversity Day observance, so please register by calling the CDER EEO Office at 301-594-6645.

Great support was provided by CDER's EEO Office, Executive Operations Staff and supervisors of the members of the 1997 Diversity Day Planning Committee, including **Margaret Bell**, **Denise Rahmoeller Dorsie**, **Dottie Pease**, **Dave Moss**, **John Purvis,** and **Mei-Ling Chen.** As planning committee chair, I would also like to thank the hard-working subcommittee chairs: **Zulema Miguele,** hospitality; **Pat Guinn,** publicity and decorations; **Marta Locklear,** cultural presentations; **Cindy Adams,** food; **Guyann Toliver,** fashion show; and **Ting Eng Ong,** exhibits.

Gloria Marquez Sundaresan is a member of the CDER EEO Staff.

Pediatrics Corner

Children and Medicines—Information Isn't just for Grownups

Victor Raczkowski, M.D., M.S.

Dr. Robert Pantell, a pediatrician at the University of California, San Francisco, asked a mother about her child's social relationships. She responded, "Johnny and Billy are over at the house all the time. I feel as if I have three children, not just one. My son has no problem with social interactions." But when her son was asked the same question, he said, "My only friends are Johnny and Billy. Everyone else at school ignores me."

Dr. Pantell recounted this story at a conference sponsored by the U.S. Pharmacopeia (USP) held last fall in Reston, VA: "Children and Medicines: Information Isn't just for Grownups." He used this anecdote to highlight a simple truth: adults and children often perceive things quite differently. To educate children about medicines, we must define the content of what the children need to know and optimize the manner in which that information is conveyed. We should also determine the settings and potential teachers. Some thoughts from the conference are summarized below.

Many children use medicines during childhood and throughout their adult lives. Therefore, they should be educated about medications. Such an education can increase a child's involvement in health care by creating an informed consumer. A child may also feel more empowered and be better equipped to understand and assess drug advertising. (Who knows, this could spark an interest that might ultimately recruit some new crackerjack FDA reviewers!)

At first glance, the content of what children need to know about their medications seems straightforward. For example, the World Health Organization has concluded that children should know the name of the medicine; the reason for using it; and how much, when, and how long to take it. Children should understand whether the medicine is working and what to do if it isn't. They should know the medicine's side effects, and what to do about them and understand the consequences of not taking their medicine or missing doses. They should also know if another medicine may be taken at the same time. Do you know this much about the medicines that you are taking?

Although such specific information about a particular medication is important, it is limited in scope. Children should receive general education about medicines, and not just learn about them through ad hoc personal experience. Even though many school health programs educate children about poison prevention or illicit drug use, few teach their students about medications in a broader context. Hence, opportunities are being missed to educate children more generally about medicines.

The manner in which information about medicines is conveyed to children is as important as the content. Children (like Johnny's and Billy's friend) often have different perceptions than adults. In addition, a child's understanding of medicines will be heavily influenced by cognitive development, coping style, personality traits, cultural beliefs, and autonomy. It can also be affected by the chronicity and severity of a child's illness. Accordingly, education about medications must be an ongoing process that continues to evolve as a child develops. Communication with children about medicines should take into account more than just the child's chronological age. Any formal educational program should be developmentally appropriate and culturally sensitive, with clear goals, outcomes, and evaluation tools.

Opportunities to teach children about medication occur in many settings, such as at home, school, the doctor's office, the pharmacy, or through the mass media or interactions with other children. Parents, physicians, nurses, pharmacists, school-health educators, hospital educators, other children, drug companies, non-profit organizations, and others can play a role. For example, as demonstrated at this conference, the USP (a private organization) is looking at the advisability and feasibility of developing, implementing, and evaluating medicine education programs for children.

Dr. Victor Raczkowski, Division of Medical Imaging & Radiopharmaceutical Drug Products, is the FDA's Ad Hoc Reviewer on the USP's Pediatrics Advisory Panel and is a member of FDA's Pediatric Committee.

Applications Sought for Emergency Use of Certain Oral Contraceptives

The FDA has published a *Federal Register* notice requesting that manufacturers submit supplemental new drug applications for emergency use of certain oral contraceptives. This use of oral contraceptives, known as emergency contraception, is intended to prevent pregnancy in women who have had unprotected sexual intercourse.

The agency issued this notice because it concluded, on the basis of current scientific evidence, that certain oral contraceptives approved for daily use are safe and effective as emergency contraceptive pills. Approval of this indication would allow information on appropriate treatment regimens to be added to the labeling for physicians and patients alike.

Although emergency contraception is not as effective as proper use of a regular contraceptive method, it substantially reduces the chances of becoming pregnant after unprotected sexual intercourse.

Risks, contraindications, and warnings for the emergency use of an oral contraceptive would be similar to those for oral contraceptives prescribed for daily use.

In the *Federal Register* notice, the agency said that it is prepared to accept applications based on the available evidence. FDA's action is part of its continuing efforts to increase the information available to patients and physicians by making "off-label" use of approved drugs part of a product's official labeling.

One New Drug, One Pediatric Use Supplement

Two Protease Inhibitors Approved for Treating HIV in Children

CDER's Division of Anti-Viral Drug Products (DAVDP) this month approved two HIV protease inhibitors—some of the most powerful medicines against the infection—for use in treating children.

Nelfinavir received its initial approval—including information on use in both adults and children—84 days after its application was received. The labeling for nelfinavir includes a pediatric use statement, giving doctors specific dosage recommendations for patients 2 to 13 years old. In addition, ritonavir, a previously approved protease inhibitor, also received pediatric use labeling in 52 days.

The pediatric use section in the drug labeling provides specific recommendations for the use of the drugs in children. A regulatory reform initiated in 1994 eased the process of including label information that helps physicians in treating pediatric patients—particularly in serious or life-threatening situations.

Now, such information can be provided when evidence suggests that the course of the disease and the effects of the drug are similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Nelfinavir received accelerated approval, a regulatory mechanism under which FDA bases early marketing approval for a product on laboratory markers such as plasma HIV RNA (a measure of viral load) and CD4 cell counts until information about clinical endpoints such as disease progression or mortality is available.

The Center based its approval of nelfinavir on studies of up to 24 weeks in duration showing that the drug was active in combination with nucleoside analogues for the treatment of HIV or if administered alone. However, because the antiviral activity of nelfinavir is increased when used with other drugs approved for treatment of HIV, combination therapy is recommended.

According to DAVDP's **Kimberly Struble,** special thanks are due to the nelfinavir review team: **Shukal Bala, Tony Carraras, Lauren Connors, Mike Elashoff, Russ Fleisher, Ken Hastings, Sherry Lard, Paul Liu, Sam Maldonado, Kellie Reynolds,** and **Nancy Sager.**

Supervisors working on nelfinavir were: **Chi Wan Chen, Gary Chikami, Tony Decicco, Jim Farrelly, Paul Flyer, Donna Freeman, Steve Gitterman, Janice Jenkins, Steve Miller** and **Jim Ramsey.**

Also a special thanks to the ritonavir pediatric supplement review team: **Barbara Davit** and **Jeff Murray.**

Project Management Corner: Fax on . . . Polite Request?

By Susan Cusack

Most of you know that OTCOM has a Fax-on-Demand system in place. Very recently, they launched an information campaign describing the system. Included in the packet I received was a magnet and telephone stickers printed with the Fax-on-Demand number (800-342-2722) and other useful information.

I have never considered myself to be a "demanding" person, but I recently decided to give it a try so I called the number (easy to find because it was stuck to my phone). Well, it turns out that you don't have to demand anything. The automated answering system gives you three choices: you can request an index of available documents, enter a document number, or actually speak to someone. I decided to request an index of available documents. Through another automated selection system, I supplied the necessary information and soon the index that I requested was printing out of my fax machine.

Drug approval information is included in the list of available documents that the OTCOM folks are responsible for "Faxing-on-Demand." This information is supplied to them by the CSO/Project Managers (PM). Upon approval of a new drug application (NDA) or an efficacy supplement, the CSO/PM sends a copy of the approval letter by fax to the sponsor. After verifying that the firm has received it, they do the following:

- FAX a copy of the approval letter to Freedom of Information, HFD-205, at 827-4576.
- Send an e-mail to OTCOM (user name "APPROVALS") containing the following information: NDA number, supplement number; name of drug; name of sponsor; indication(s); whether it is a new dosage form or route of administration; whether it is an Rx, OTC, or an Rx-to-OTC switch; and drug classification and priority rating.

Susan Cusack is a consumer safety officer in the Division of Medical Imaging & Radiopharmaceutical Drug Products.

Mentor's Corner: Project Mentoring

By June Cory

Joy Mele, who is a member of the Mentor Advisory Group as well as a Biostatistics Reviewer, reports that she likes to work with a new reviewer protege by arranging with the Team Leader for her protégé to be assigned a project which is a part of Joy's NDA assignment.

In this way, the protégé has a specific assignment around which to focus learning the review process, and Joy gets some help with her NDA assignment. Thus, both mentor and protégé benefit from this approach. If you would like more information about how this can be worked out, call Joy Mele at 443-3520.

June Cory is a member of the Division of Training and Development.

Reviewer Affairs Corner: Handy Handbook Published

By Karen Oliver

One of our 1996 finished products is the *CDER Reviewer Affairs Committee (RAC) Handbook.* Members of the Operational Procedure Subcommittee, chaired by **Karen Lechter,** drafted, revised, finalized, and distributed the green notebook to your RAC representative last month.

The contents of the handbook will acquaint you with some basic RAC information including bylaws, RAC representative duties, a roster of division representatives, historical documents, subcommittee descriptions, subcommittee rosters, minutes of the quarterly meetings with Center management, a list of the contents on RAC's X:drive subdirectory, and the most recent RAC annual report. Please take a few minutes to browse through the notebook and use it as a resource. If the location of the handbook is a mystery to you, please ask your RAC representative (see February *Pike,* page 6); he or she has the only copy for your division and is responsible for its upkeep. The handbook will be passed along to successive representatives.

In the meantime, other RAC subcommittees are working for you on such topics as mentoring, comparable pay, a survey of reviewers, and a reviewer's handbook. You do not have to be a member of the RAC to serve on one of its subcommittees so check the handbook at Tab 4, find a project that interests you, and contact the subcommittee chairperson to volunteer. Please e-mail your kudos, constructive criticisms, questions, or comments (OLIVERK) and copy to **Janet Higgins** (HIGGINSJ), chair of the RAC.

Karen Oliver is a regulatory health project manager in the Division of Gastrointestinal and Coagulation Drug Products.

Rubber Hits Road at OPS-Conducted ICH Industry Training

(Continued from page 1)

long haul.

- Trade and economic interests. In an era of increased global trading, unique national standards could eventually be viewed as trade barriers.
- The drive for efficiency. Governments across the world are under pressure to provide more timely reviews with fewer resources.

"The reasons for ICH are immediately apparent if you are global," echoed Deputy Center Director for Pharmaceutical Sciences **Roger Williams.** The ICH process of industry and regulators working together will create "a profound set of documents with a global impact," he said. He called the current situation in which each country has its own requirements "an unacceptable way to do business." He said that the approximately 90 people in CDER working on ICH issues were doing it as an extra duty beyond their review responsibilities.

Williams pointed out that the guidances that result from the ICH process are not legally binding on either the Agency or the industry. For the Agency, Williams emphasized that the guidelines represent a ceiling. While reviewers need to exercise their professional and scientific judgments, they won't routinely ask industry to provide more information than called for in the ICH documents unless there is a sound scientific reason in accordance with good guidance practices. While industry can always propose an alternative approach when necessary, they may have to provide justification for approaches not outlined in the ICH documents. In the United States, the guidelines are in effect when they are published in the *Federal Register.* Nonetheless, Williams pointed out that industry needs time to adapt to new procedures and in some cases purchase and install new equipment. For several of the documents discussed at the training session, officials in each of the three regions reached certain agreements to begin using the new guidelines next January.

Williams explained the structure of the ICH. At the top echelon, the ICH steering committee has 14 members. Two regulatory officials from each region and two trade association representatives from each region hold 12 seats, and the other two seats are held by the International Federation of Pharmaceutical Manufacturers Associations.

The first areas where harmonization was sought are called *efficacy*, *safety* and *quality*. What ICH calls "efficacy," we know as clinical safety and efficacy. Similarly, the area ICH calls "safety" is known to us as preclinical safety testing, and "quality" is our production control or good manufacturing practices. As the ICH process developed, a fourth area, a multidisciplinary one covering *regulatory communications*, was added to focus on medical terminology and electronic standards for the transmission of regulatory information and data.

A shorthand method of referring to the documents by a letter, number and letter combination has developed. The shorthand uses "E" for efficacy, "S" for safety, and "Q" for quality guidelines; and "M" is used for regulatory communications. For example, the three Q1 documents concerning stability testing are known as Q1A, Q1B, and Q1C. There are 44 specific ICH guidelines identified so far.

Each ICH guideline goes through a five-step process from birth to formal adoption:

Step 1. An expert working group develops a draft consensus on a topic.

Step 2. The regional authorities, for example CDER, circulate the draft and obtain comments from citizens, industry, academia and others.

Step 3. The expert working group revises the draft and passes it on to the steering committee.

Step 4. The steering committee discusses the guideline and hands it over to the regional regulatory bodies.

Step 5. The process is complete when the regulatory bodies

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CDER Forum: Televised Brown Bag Lunch Series Kicks Off

Bring your lunch, bring your co-workers and bring your questions and comments every Tuesday to the CDER Forum at noon. Hot topics of interest to CDER will be televised to CDER's videoconferencing sites (Corporate, S-100; Woodmont, Conference Room G; Parklawn 13B-37) for your convenience.

The CDER Forum is a series of focused weekly 45-minute discussions that will be presented and lead by a CDER expert.The speaker will present a 15- to 20-minute overview on the topic and the remainder of the time will be spent on your questions and answers, as well as on listening to your comments.

"The CDER Forum is an informational series aimed at increasing our understanding of the entire CDER community regarding the contributions made by different organizational units, and at enhancing communications about subject-matter topics of current interest," said **Mary Lambert,** OTCOM Special Assistant.

The announcement of this program has received an enthusiastic response from the Center via e-mail. In fact, the subject-matter topics were suggested by CDER employees. On March 18, Center Director **Janet Woodcock** launched the series by outlining challenges facing the Center; and on March 25, **Carol Assouad** discussed plans for the CDERnet.

Future dates, speakers and topics include:

- April 1, **Jane Axelrad,** Good Guidance Practices.
- April 8, **Nancy Smith,** Master Reviewer Program.
- April 15, **Nancy Smith & Zan Fleming,** *Virtual Journal*.
- April 22, **Lisa Rarick** and **Janet Woodcock,** Product Labeling—Pregnancy Categories.
- April 29, **Janice Newcomb,** Training and Development Initiatives.
- May 6, **Mary Lambert,** CDER's New Honor Awards.

OPS Shines at ICH Training

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Step 5. The process is complete when the regulatory bodies in each region incorporate the guidelines into their regulations, which in our country means that each guideline goes through a notice-and-comment rulemaking to be published as a final rule in the *Federal Register.*

Judy Boehlert, the chair of the industry training committee, presented an industry perspective on the ICH guidelines. She noted that consensus building was a give-and-take process that requires all parties to make some compromises. Boehlert emphasized that industry will need a consistent interpretation and implementation of the guidelines in the three regions and by both FDA reviewers and field investigators. She pointed out that there is no mechanism through which to work out issues that were unresolved in the consensus building process.

OPS's **Charles Hoiberg** said the "rubber meets the pavement" in the seven quality documents that have reached steps four and five. Once the guidelines go into effect when published in the *Federal Register,* the process shifts from one of development to one of training, implementing and managing. Although not all-inclusive, the guidelines form a core around which will evolve guidances to industry and review practices within the Center.

Following the overview were three technical sessions on stability, impurities and analytical methods. Each session consisted of a series of technical presentations, a videotaped "case study" and a question-and-answer forum with a panel of experts.

Chi-Wan Chen discussed two guidelines concerned with stability testing of new molecular entities, new drug products and new formulations of already approved drugs. She emphasized that the documents provide "core" data on the shelf life of drug products. **Thomas P. Layloff** discussed a document on photostability: how medicines are affected by exposure to light. Neither the European Union nor the United States had photostability standards before ICH, but both liked those developed by the Japanese so they were adopted.

Kasturi Srinivasachar and **Eric P. Duffy** presented the guideline on impurities in new drug substances, that is, impurities that result from the manufacture of the active ingredient itself. The guidelines cover the identification of the impurities, their quantification and reporting requirements. **Albinus D'Sa** reported on the guideline covering impurities that either result from the degradation of the drug or are present in the other ingredients in the drug product. **Linda Ng** discussed the guidelines covering the accuracy and precision of the laboratory tests used to determine stability and identify impurities.

In addition to those making technical presentations, other FDA members in the panel discussion groups included **Diana Kolitis, Kenneth Furnkranz, Frank Holcombe** and **Eric Sheinin.**

A humorous chord was struck when an industry chemist suggested that the FDA require America's refrigerator manufacturers to build a home medicine cabinet into their products. That way, he suggested, strict stability requirements for his delicate molecules could be relaxed.

Information about the ICH process and topics under development can be found on the ICH Internet site located through the PharmWeb home page: http://www.pharmweb.net. ICH guidelines in their final steps with information about their *Federal Register* publication are available on CDER's Web site under regulatory guidances.

Public Input Sought on Ozone-Depleting Propellant Plan

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products (which are the only permitted commercial use for CFCs in developed countries since Jan. 1, 1996), the pharmaceutical industry has been working for the past decade to develop alternative inhalation products that do not use CFCs. The Center's Division of Pulmonary Drug Products has been working closely with the pharmaceutical industry to facilitate development of safe and effective alternative products. The first MDI with an alternate propellant was approved by FDA in August 1996 (Proventil HFA, an albuterol sulfate MDI) and industry officials project that NDAs for over 30 alternative products (including alternative propellant MDIs and other inhalation dosage forms such as dry powder inhalers) could be submitted to the Agency by the year 2000.

The transition strategy proposed in the ANPRM is designed to phase out the CFC essential use exemptions as alternatives become available and prove to be acceptable replacements for the current CFC products, including acceptability to patients. The overall goal of the strategy is to allow a "seamless" transition for patients and physicians. Since this is an important and controversial area, Center officials are seeking the broadest possible public input in developing the transition strategy by publishing the proposed strategy in the form of an ANPRM rather than a proposed rule.

The comment period for the ANPRM is for 60 days following March 6. On April 11, there will be a Pulmonary and Allergy Drugs Advisory Committee meeting on the proposed strategy.

The CDER CFC Work Group members are: **Tunde Otulana, M.D.,** medical officer in the Division of Pulmonary Drug Products (DPDP) and chair of the work group; **John Jenkins, M.D.,** Director, DPDP; **Parinda Jani,** project manager, DPDP; **Joseph DeGeorge, Ph.D.,** Office of Regulatory Management, Pharm-Tox; **Christina Good,** Office of Legislative Affairs; **Susan Johnson,** Pharm.D., medical reviewer DPDP; **Robert Meyer, M.D.,** medical team leader, DPDP; **Rashmikant Patel, Ph.D.,** Office of Generic Drugs; and **Guirag Poochikian, Ph.D.,** chemistry team leader, DPDP. Also contributing to the development of the ANPRM: **Martin Himmel, M.D.,** Deputy Director, DPDP; **Joseph Sun, Ph.D.,** pharmacology team leader, DPDP; and **David Tishler,** Office of Policy.

Aims at Simplifying Review Process

Center, FDA Publish Draft Clinical Evidence Guidances

The FDA this month proposed a New Use Initiative to speed up the development of new and supplemental uses of medications by using all available data to determine the effectiveness of drugs and biological products.

FDA's initiative gives industry clear guidance on when the Agency can determine that a drug is effective for a new use without requiring data from two new clinical trials. For example, in some cases a drug's effectiveness can be extrapolated from existing efficacy data; it can be shown by evidence from a new single trial supported by already existing related clinical data; or it can be documented by adequate evidence from a single multi-center study.

"The science of drug development and clinical evaluation has evolved so significantly that we now have more ways to determine the benefits and side effects of new drugs," said **Michael A. Friedman, M.D.,** FDA's Lead Deputy Commissioner. "This initiative outlines how we can simplify the approval process while continuing to uphold standards that have earned the public's confidence."

Under the initiative, two new guidances are being made available for comment. Both documents are available on CDER's Web site.

One of them, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* outlines the general policy. The other proposal, *FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products,* clarifies what evidence can be sufficient for supplemental applications for cancer treatments and describes steps the FDA is taking to foster the updating of labeling for products used in cancer treatment.

"Our proposal does not lower FDA's commitment to high effectiveness standards: it identifies situations in which multiple new clinical trials are not needed," said Center Director **Janet Woodcock, M.D.** "In some instances, we can rely on published scientific reports."

The guidances cite several instances in which FDA has approved new or additional product uses on data other than that collected during new multiple trials.

For instance, when the course of the disease and the beneficial effects of the drug are sufficiently similar for both adults and children, the agency has allowed the Pediatric Use section of product labeling to include information extrapolated from adult efficacy data.

Examples of such pediatric labeling include ibuprofen, a non-steroidal anti-inflammatory drug, and ondansetron, a treatment for chemotherapy-induced nausea.

In the case of enalapril, a drug for heart failure, the agency accepted two different effectiveness findings, each from a different study, one of which showed symptom improvement and the other improved survival. The drug was approved for both treatment of symptoms and improving survival.

The Clinical Evidence guidances, however, caution that care should be taken when relying on a single clinical trial, and stress that the quality of scientific evidence is as important as its quantity.

The Agency will continue to explore how to improve the supplemental application process for sponsors of all approved products with promising but unlabeled uses.