news along the pike

January 1997

Center for Drug Evaluation and Research

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Pike's Corners . . .

FDA Proposal

Withdraw Seldane from U.S. Market

The FDA announced in a Jan. 14 *Federal Register* notice its intention to withdraw the approval of Seldane (terfenadine), Seldane D (terfenadine and pseudoephedrine) and generic versions of the prescription antihistamine. The FDA, with the advice of Center officials and the Division of Pulmonary Drug Products, has determined that drugs containing terfenadine are no longer shown to be safe because Allegra (fexofenadine) is now available.

FDA recently approved Allegra, which contains fexofenadine, the primary active derivative of terfenadine produced in the body when terfenadine is taken. Fexofenadine provides nearly all of terfenadine's beneficial effects but does not appear to cause a potentially fatal heart condition when taken with some other commonly prescribed medications.

Introduced in l985, terfenadine is marketed by Hoechst Marion Roussel (HMR) of Kansas City, Mo., and was the first prescription antihistamine to relieve the symptoms of allergic rhinitis without causing drowsiness. Following approval, FDA received reports of serious and sometimes fatal cardiac arrhythmias associated with terfenadine when it was taken with some other medications or by patients with liver disease. These other drugs, such as erythromycin (an antibiotic) and ketoconozole (an antifungal drug), can cause terfenadine to build up in the blood and result in serious cardiac side effects.

Since the serious cardiac risks of terfenadine were identified, several educational campaigns have been launched by the drug's sponsor and the FDA to inform health care providers and patients about the dangers of these drug interactions. These have included FDA warning statements, labeling changes and "Dear Doctor" letters. Although these efforts have reduced inappropriate prescribing and dispensing of terfenadine with other drugs, such events have not been, and almost certainly cannot be, entirely eliminated.

Prior to the approval of fexofenadine, the Center considered the benefits of terfenadine to outweigh its risks despite its known serious cardiac adverse effects when used inappropriately.

Hoechst Marion Roussel developed Allegra, which was approved in July l996. HMR said in a press release that it intends to defend Seldane and stands behind its safety when used according to the label.

Now that fexofenadine is available and provides the therapeutic benefits of terfenadine without the associated serious cardiac risks, terfenadine's benefits are no longer considered by the FDA to outweigh its risks. In view of these developments, the FDA has determined

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Kessler Lauds CDER During FDLI Address

David A. Kessler, M.D., focused on CDER's achievements in getting important new therapies to patients who need them during a major portion of his last major address as FDA Commissioner to the Food and Drug Law Institute at their Dec. 10 annual meeting.

"The one number that has, over the years, been an important symbol is the number of new molecular entities approved in a given year," Kessler said in his prepared remarks. "In essence, a new molecular entity is 'an active ingredient that has never been marketed in this country.' The number of NMEs is a sign of hope."

For calendar year 1996, CDER's Office of Review Management reported in early January that the Center approved a record 53 NMEs,

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Joe's Notebook

Words and Things

One of my favorite stories concerns Degas and Mallarmé. One day the painter Degas, with a handful of his attempts at poetry, goes to his friend, the poet Mallarmé. Degas says: "Here, Mallarmé, help me fix these. I have such great ideas, but I can't make them come out in sonnets." Mallarmé replies: "My dear Degas, you don't understand. A poem isn't made from ideas, it's made from words."

Poets and scientists, and editors, too, know that words are tricky things to work with. Sometimes they lead us to think we know more than we do. A particular set of signs and symptoms gets the name of a disease or syndrome, and a collection of words, a body of medical "literature," builds up around it. But, is that syndrome really one disease? The poet and scientist are at two ends of a spectrum when it comes to words and things. The poet frequently depends on a word's ambiguities. The scientist wants to stamp out ambiguities and use words precisely.

Most of us fall somewhere between either end of the spectrum. When we use a word for something, we often think we have a handle on what we're talking about. When we do that, we are in danger of putting the cart before the horse—trying to get a handle on the thing before we get a handle on the word. Well, **Bill Hess,** the Center's lexicographer, knows all about how CDER is trying to get a handle on the words it uses. He also tells us about the benefits to the review process, both for industry and for reviewers. The Nomenclature Standards Committee debuts its Corner in this month's *Pike.*

Two other groups, Reviewer Affairs (talk about ambiguous words) Committee and Administrative Management Coordinating Committee take their inaugural bows as well. Be sure to welcome their authors **Charlene Cherry, Kristin Crown** and **Karen Oliver** to the *Pike.* Other contributors, **Rose Cunningham, Wendy Cheng, Kathleen Alt, Margaret Bell, Linda Brophy, Russ Abbott** and **Lydia Kause** join forces on this month's issue with regular contributors **Jim Morrison, Susan Cusack, L. Miriam Pina, M.D., Gloria Marquez Sundaresan** and **Diane Smith.**

Lydia Kaus in the Reviewer's Corner highlights some of the inevitable trade-offs we make between improving our managerial skills and our technical skills. If the overflow crowd at the first of this year's scientific seminars is any indication, a large number of us are taking **Zan Fleming's** admonition to heart to do some "saw sharpening." The thought provoking seminar was led by **Robert H. Rubin, M.D.,** and his colleagues **Stan N. Finkelstein, M.D., Thomas J. Allen, Ph.D.,** from the Health Sciences and Technology Center for Experimental Pharmacology and Therapeutics run jointly by Harvard University and the Massachusetts Institute of Technology.

The presentation, "Drug Development for the 21st Century," focused on how academia, industry and government might forge a tighter partnership to deal with the revolutionary discoveries of modern molecular and cellular biology and the unprecedented flow of new compounds with potential disease modifying activity that are being pumped into the pipeline. The presentation promoted lively discussion. If there is a tension between words and things, a similar tension between rational and empirical models of drug development was noted by a number of discussants, including **Bob O'Neill** and **Satya Dubey** from the Office of Epidemiology and Biostatistics and former Center Director **Carl Peck.** From the regulatory point of view, Peck and others pointed out, the final gateway remains adequate and well-controlled empirical studies.

news along the pike

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

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

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

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

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Ombudsman's Corner

When the 'R' Word Rears Its Ugly Head

By Jim Morrison

Most of us at some time in our lives have been in the uncomfortable position of being accused of doing something we didn't do. When that situation arises, it is often impossible to prove that we didn't do a particular thing or, if we did it, that we didn't do it with the alleged motive. Such is the nature of defending ourselves or our organization against charges of retaliation. Unfortunately, CDER has had to do just that before Congress in recent years.

In the context of a regulatory agency, retaliation is usually defined as a regulator taking action, or not taking action, to the detriment of a regulated individual or company in reprisal for some previous action by that individual or company. Even an implied threat to retaliate is considered retaliation.

To use an example that might occur in CDER, Company A submits an NDA to CDER. There follows a scientific dispute about the review, which the company appeals to the office level, and the office director agrees with the company. A subsequent NDA that Company A submits to the same review division receives a not approvable letter citing numerous deficiencies requiring a lot of time and money to resolve. Company A charges that the division was overly picky on the second application in retaliation for the company's appealing the earlier dispute. The division maintains that its deficiency letter was entirely appropriate.

Obviously, there is no real defense that anyone in the division can offer to erase the perception of retaliation in the minds of the applicant and of those who want to believe that retaliation is part of the way we do business. The only way I know to reduce the likelihood that anyone will allege retaliation is to build trust by incorporating three simple customer service principles in all our contacts.

First, from my observation, the most important principle of good customer service is expeditious response. Nothing gets relationships off to a worse start than failing to return phone calls promptly or not answering letters. In addition, stating an approximate time in which a substantive answer can be expected, if one cannot be given right away, and meeting that time frame proves that our word is good and that we can be trusted.

CDER has already done much to establish a track record in timeliness. The entire Prescription Drug User Fee Act implementation has improved our relations with the public and with the regulated industry enormously. We need to extend that success to all aspects of our work.

Second, the response should be fair, reasonable and well thought out. If we give a quick response that is inappropriate, requires further explanation or seems inconsistent with other decisions, we convey a careless attitude and undermine our own credibility.

Third, the manner in which business is conducted should convey an understanding and caring attitude. This factor is more difficult to measure than the first two because it is subjective. It involves much more than a pleasant voice on the phone or a well-written letter. Customers look for evidence that the person they are dealing with understands their problem and cares about the outcome.

Everyone who comes to us has a problem, whether it is a company that needs our approval to market a product or a consumer who has had a bad experience with a drug product. If we respond to all our contacts promptly, take the effort to understand each person's problem and provide a fair, reasoned answer in a timely and appropriate manner, I guarantee you that charges of retaliation against CDER will be only bad memories.

For more information about retaliation, please refer to FDA Commissioner David A. Kessler's memo to all FDA employees dated June 29, 1995, available on the Internet at:

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

Jim Morrison is the Center's Ombudsman.

Rheumatoid Arthritis Guidance Slated for Public Comment

By Rose Cunningham

In an ongoing effort to obtain as much input and consensus as possible for a revised guidance document for rheumatoid arthritis, the Intercenter Rheumatology Working Group has scheduled a public discussion of the document during the Arthritis Advisory Committee meeting Feb. 5, Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, 8 a.m. to 5 p.m.

The first draft of this document was discussed during two public workshops in 1996. These workshops were well-attended and productive. The working group received invaluable input from industry and academia regarding document format, desired guidance and content concerns. The current revision is a result of these workshops and continuing discussions of the working group which has representatives from CBER, CDER and CDRH. They are seeking the Advisory Committee's input on the document before completing a final draft for publication in the *Federal Register*.

The draft document is available on the Internet. From CDER's home page (http://www.fda.gov/cder) pick Regulatory Guidance, then Guidance Documents, then scroll to Clinical/Medical-Draft. The draft document is in Adobe PDF format (http://www.fda.gov/cder/guidance/raguide.pdf).

Rose Cunningham is a regulatory health professional in the Office of the Center Director.

Administrative Management Corner

New Coordinating Committee Eyes Center Administration

By Charlene Cherry and Kristin Crown

The Administrative Management Coordinating Committee (AMCC) is a culmination of the efforts of the Administrative Functions Work Group (AFWG)—a group formed during the 1995 CDER restructuring initiative to review and revise administrative functions and delegations in the Center. The AMCC expands on the charge of the AFWG to streamline administrative functions and develop guidelines that can be consistently applied throughout the Center.

The AMCC membership represents the entire Center. Subcommittees of the AMCC represent eight primary administrative functions in the Center: human resources, facilities, budget/procurement, travel, training, payroll, information technology for administrative issues, and a users group. The users group is made up of the senior management officers from each office and will address broad administrative issues that filter up from the offices and have an impact on the Center as a whole. Subcommittees are chaired by a permanent voting member of the AMCC. The role of each subcommittee is to provide advice and assistance to the AMCC when responding to CDER staff on administrative issues. Each subcommittee is charged with doing a comprehensive review of all administrative processes in their respective area. Streamlining of administrative functions is the ultimate goal.

You can provide input about your concerns relating to administrative issues to any AMCC member. Subcommittees also need members. Please contact the subcommittee chairpersons if you are interested in serving on one. AMCC members are:

- **Paula Bourkland,** Office of Management, AMCC chairperson and User Group Subcommittee chairperson, 594-6741.
- **Charlene Cherry,** Office of Management, AMCC executive secretary, 827-0517.
- **Ruth Clements,** Office of Management, Facilities Subcommittee chairperson, 594-2420.
- **Patricia DeSantis,** Office of Review Management, co-chairperson Human Resources Subcommittee, 594-5465.
- **Denise Rahmoeller Dorsie,** Office of Review Management, Information Technology for Administration Subcommittee chairperson, 594-5479.
- **Tanya Abbott,** Office of the Center Director, Human Resources Subcommittee co-chairperson, 594-6779.
- **Laurie Watson,** Office of Pharmaceutical Sciences, Travel Subcommittee chairperson, 443-0260.
- **Rich Vengazo,** Office of Pharmaceutical Sciences, Payroll Subcommittee chairperson, 594-5476.
- **Anita Harrell,** Office of Compliance, Budget/Procurement Subcommittee chairperson, 594-1058.
- **Linda Brophy,** Office of Training and Communications, Training Subcommittee chairperson, 827-1651.

MAPP 7800.1 describes the AMCC in more detail.

Charlene Cherry is the Branch Chief, Management Analysis Branch, Division of Planning Evaluation and Resource Management, and Kristin Crown is a management analyst in the branch.

Project Management Corner

Are We Keeping Up with Du Ponts . . . or Lillys . . . or Glaxos?

By Susan Cusack

Did you ever wonder how project management at CDER compares to that in the drug industry? Are we implementing project management on the same scale or to the same degree? Or are we, CDER's project managers, struggling to keep up?

In November, **Susan Kummerer,** acting supervisory CSO in the Division of Medical Imaging and Radiopharmaceutical Drug Products, and I had the opportunity to find out. We presented "Project Management at the FDA," part of a course offered by the Pharmaceutical Education and Research Institute (PERI) called "Current Topics in Project Management."

Susan's remarks included a brief history of the project management initiative at CDER, an outline of PDUFA goals and achievements, as well as a description of the dual role of project manager and regulatory affairs manager that consumer safety officers at CDER play. I focused more directly on how project management is currently implemented. Our take-home message was that CDER is striving to be accessible and to work in collaboration with industry. CSOs and project managers, as the points of contact for industry, play a vital role in this collaboration.

So, after a three-day look at the other side, are we keeping pace with industry? The answer is a resounding "Yes!" Both from the formal presentations and informal discussions, Susan and I were able to gain some insight into how project management is implemented in a variety of different companies. As in CDER, people in industry employ a wide range of project management tools; everything from yellow stickups on a wall to elaborate computer programs. Most companies are gradually moving to some electronic method of tracking projects, but a surprising number aren't there yet.

I am confident that we will continue to "keep up with the Du Ponts" as long as we strive to find better, more efficient ways of managing the drug review process. As always, if you have any ideas to share, please send me an e-mail message (CUSACKS).

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

AMF Corner

Reference Books Coming to Your Windows Desktop

By Wendy Cheng and Kathleen Alt

The Automated Management of Files (AMF) project has several major components that support electronic access to the information we need during the review process. In issues throughout 1996, you have seen updates for these major components such as the efforts to provide friendlier interfaces to CDER databases (May, August, October and December), the Excalibur labeling and review document repositories (June and July) and the Division File Document Management System (November).

The most recent addition to the AMF family of products is an upgraded version of the Library Electronic Reference Network (LERN) system. The new WinLERN system lets you access the Medical Library's CD-ROM titles directly from your personal computer in a more user friendly, Windows-based manner. It provides a startup icon on your desktop to access three different menus: Biomedical, Legal/Regulatory and General Reference. The icons within each menu are associated with a CD-ROM title. Some examples of the reference tools you can access are *Medline Express*, the *Physician's Desk Reference*, the *Food and Drug Library* and the *Encyclopedia of Associations.*

In the next few months, the Library's user education team and communications team will be putting together documentation on using the various search interfaces of the WinLERN CD-ROM titles.

WinLERN is easy to use and provides access to many of the CD-ROM reference databases in one location on the CDER network. The WinLERN installation procedure also automatically performs all the required installations. Once you access the CD-ROM reference titles via WinLERN, you will be able to:

- Cut and paste the text and, eventually, graphics from the CD-ROM titles to another application such as Notepad or Word.
- Print the text or graphics from the database windows.
- Download citations directly to your hard drive or floppy disk.

LERN itself is going to undergo a series of transformations this year. WinLERN is an interim step in getting Windows-based CD-ROM titles available to CDER's PC users. In conjunction with DISD, the Library will be upgrading LERN equipment in the spring and then bring all LERN titles up with a web-browser front end on the Library's home page on CDERnet.

Access to WinLERN is now being phased in starting with CDER staff in Parklawn. We hope to have it available to all CDER staff with Windows 95 on their PCs by the end of February. For more information about WinLERN please e-mail Wendy Cheng (CHENGW).

Wendy Cheng, a librarian in the Medical Library, and Kathleen Alt, an AMF contractor, authored this month's AMF Corner in cooperation with regular author David Isom.

Pediatric Rule Extension Granted; Nasalcrom Goes OTC

The FDA granted a pharmaceutical industry request for an extension to the Pediatric Rule deadline. Manufacturers now have until April 7 to comply with the rule if they notify the Center in writing by Jan. 23 of their intent to submit a labeling supplement with more complete information about the use of a drug in the pediatric population. The rule requires sponsors to reexamine existing data to determine whether the "Pediatric Use" subsection of the labeling can be modified based on adequate and well-controlled studies in adults and other information supporting pediatric use. The original date for drug sponsors to submit appropriate supplements was Dec. 13.

Pulmonary Drugs Scores Double First with Nasalcrom

When the Division of Pulmonary Drugs cleared Nasalcrom (cromolyn sodium) for over-the-counter marketing, they approved the Center's first NDA of the year and the first nonprescription nasal spray that specifically helps prevent and treat symptoms related to nasal allergies. Cromolyn sodium can be used regularly by adults and children, age 6 and older. When used prior to allergen exposure, such as before the start of the hay fever season, cromolyn sodium is effective in diminishing allergic nasal symptoms.

The review was a joint effort between the Division of Pulmonary Drug Products, the Division of OTC Drug Products, the Division of Drug Marketing, Advertising and Communications, Office of Compliance and the Division of Scientific Investigations. Key members of the review team were: **Babatunde Otulana, Bob Meyer, Jim Gebert, Steve Wilson, Vibhakar Shah, Linda Ng, Guirag Poochikian, Soo Choi, Joe Sun, Brad Gillespie, Dale Conner, Parinda Jani, Cathie Schumaker, Linda Hu, Debbie Bowen, Karen Lechter, Joan Hankin, Dave Doleski, Gus Turner, Shirnette Ferguson, John Singer, Christine Marmara.**

Pediatric Corner

Center IDs Top 10 Drugs Used Off-Label in Out-Patient Setting

By L. Miriam Pina, M.D.

After the Final Pediatric Rule was published in December 1994, the Pediatric Use Survey Working Group of the Pediatric Subcommittee was formed. The group's first charge was to identify the drugs most widely used in pediatrics on an out-patient basis for which there was inadequate use information.

Results of the survey disclosed that most drugs that are indicated for diseases occurring in both adults and children have very little information about pediatric use in the labeling. Some age groups have less information available to them than others. The population of less than 2 years of age, for instance, has virtually no pediatric use information on drug products in several class categories. In general, drugs used to treat diseases like asthma, and seasonal and perennial rhinitis, so common in children, present very little information about pediatric drug use. For other therapeutic areas, such as infectious diseases, the pediatric information is, in contrast, quite good.

The working group analyzed survey data from IMS America, Ltd., to provide estimates for pediatric use for 1994. The IMS database is an ongoing pharmaceutical marketing research survey describing drugs mentioned during patient contacts by a nationwide panel of office-based physicians randomly selected from the American Medical Association and the American Osteopathic Association (more than 2,940 physicians representing 27 specialties).

Data collected from the panel are projected nationally by multiplying the raw number of mentions in each stratum, defined by region and specialty, by a corresponding projection factor.

The table displays the drugs that were most widely used off-label in the pediatric population in 1994, according to the IMS database. The drugs are presented in order of frequency of mentions per year and reflect neither the severity of the diseases being treated nor the adverse events reported. Also, for drugs used to treat chronic conditions, the number of mentions may not correlate well with the number of patients being treated. In the chronic use of the Schedule II drug Ritalin, for example, the physician is required to prescribe it with no refills under close surveillance (the prescribing requirements vary from state to state). Thus, in this case, the number of appearances will be overestimated when compared with other drugs used chronically. Nonetheless, in every case, the physician had to make a decision to use the drug with inappropriate pediatric use information.

Members of the Pediatric Use Survey Working Group are: **L. Miriam Pina, M.D.,** chairperson, Division of Pulmonary Drug Products; **Kimberly Struble,** Division of Anti-Viral Drug Products; **Linda Hu,** Division of Over the Counter Drug Products; **Jonca Bull, M.D.,** Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products; **Cazimiro Martin,** Division of Over the Counter Drug Products; **Frank Rosa,** recently retired from the Division of Pharmacovigilance and Epidemiology; and **Charles Maynard,** Division of Pharmacovigilance and Epidemiology. The December *Pike* lists representatives from each of the Center's review divisions who can assist you with Pediatric Rule issues. The working group plans on publishing in-patient data in a future issue.

L. Miriam Pina, M.D., is a visiting scientist in the Division of Pulmonary Drug Products.

Product	Indication(s)	Label Statement	Off-Label Prescribing Frequency	Prescriber's Specialty (percentage)
Albuterol inhalation solution for nebulization (albuterol sulfate, 0.083 mg/ml)	Prevention and relief of bronchospasm.	Safety and effectiveness (S&E) have not been established in children below 12 years of age.	1,626,000 to children <12 years old.	Pediatricians (62%) Family practitioners and allergists (20%)
Phenergan (promethazine HCl)	Relief of diverse allergic reactions.	Should not be used in children below 2 years of age.	663,000 to children <2 years old.	Pediatricians (82%)
Ampicillin sodium for intravenous or intramuscular injections.	Infections due to susceptible organisms.	S&E have not been established in infants and children under the age of 12.	639,000 to children <12 years old.	Pediatricians (88%) Most common indication: perinatal infections

Product	Indication(s)	Label Statement	Off-Label Prescribing Frequency	Prescriber's Specialty (percentage)
Auralgan otic solution	Prompt relief of pain of acute otitis media and to facilitate the removal of excessive or impacted cerumen.	No instructions for pediatric use at any age.	600,000 to children <16 years old.	Pediatricians (62%) Family practitioners (23%)
Lotrisone cream (clotrimazol 1%, betamethasone dipropionate 0.05%)	Topical treatment of particular dermal, fungal infections.	S&E in children below the age of 12 have not been established.	325,000 to children <12 years old.	Pediatricians (51%) Family practitioners (24%)
Prozac (fluoxetin HCL) pulvules and liquid	Depression and obsessive compulsive disorders.	S&E in children have not been established.	349,000 to children <16 years old. Note: was mentioned to 3,000 infants <1 year of age were in 1994.	Psychiatrists (81%) Most common indication: depressive disorders
Intal (cromolyn sodium).	Prophylactic agent in the management of bronchial asthma.	For inhalation (nebulization) solution, S&E below the age of 2 have not been established. For inhalation aerosol solution (MDI), S&E have not been established below the age of 5.	Intal inhalation solution was prescribed 109,000 times to infants <2 years of age. Intal inhalation aerosol (MDI), 399,000 times to children < 5 years.	Pediatricians (71%)
Zoloft (sertraline HCl)	Depression.	S&E have not been established in children.	248,000 for children <16 years.	Psychiatrists (72%)
Ritalin tablets and sustained-release tablets (methylphenidate HCl) *(Schedule II drug)*	Treatment of attention deficit disorders and narcolepsy.	S&E have not been established in children <6 years of age.	226,000 to children <6 years old.	Pediatricians (47%) Psychiatrists (26%)
Alupent Syrup (metaproterenol sulfate).	Bronchodilator for bronchial asthma and for reversible bronchospasms.	Clinical trial experience in children under the age of 6 is limited.	184,000 to children <6 years old.	Pediatricians (59%) Family practitioners (23%)
Beclomethasone dipropionate nasal sprays (includes Beconase AQ and Vancenase AQ nasal sprays).	Relief of symptoms of seasonal and perennial rhinitis and for the prevention of recurrence of nasal polyps following surgical removal.	S&E in children below the age of 6 have not been established.	174,000 to children <6 years old.	Pediatricians (46%)

Nomenclature Standards Corner

Standardization Aims at Improving Data Management

By William A. Hess

Nomenclature control is essential to the successful operation of individual information systems and ensuring compatibility among numerous information systems. The Federal Government has recognized this for quite some time. When our nation's leaders saw the information explosion proceeding on an exponential rather than a linear scale, Congress mandated development of Federal Information Processing Standards.

CDER's leadership also recognized a similar need and set up the Nomenclature Standards Committee (NSC) to focus on how key product data is represented in our databases. The committee's work aims at improving our ability to successfully store, link, retrieve and report information from all points within the Center. The impact can be fully appreciated only when you consider that we maintain hundreds of databases, some centralized and others on individual PCs.

The NSC, which requires members representing each office, meets every two months to consider additions or changes to nomenclature standards for data elements. An example of its work includes establishing and modifying nomenclature specifications for a drug's non-proprietary name, dosage form and route of administration. The NSC also develops definitions for each of the terms in each data element to minimize ambiguity. In addition, the NSC develops nomenclature policy for the Center.

Monographs for both data elements and policy are found in the *CDER Data Standards Manual*, available from NSC committee members. Alternatively, you can find them on the X:drive in Oldxdrv\Standard. They are also scheduled to be placed on CDER's intranet and Internet sites.

The current composition of the NSC consists of chemists, computer programmers, a database administrator, pharmacists, project managers and technical information specialists. Past representation has also included pharmacologists and medical officers. The NSC works closely with the Labeling and Nomenclature Committee, which focuses more on a product's labeling rather than on how key product data are represented. The NSC also works closely with the Data Standards Committee, which is its counterpart at the Agency level. The NSC welcomes input on prioritizing particular data elements for CDER and especially encourages input from office directors, division directors and information technology focal points. The NSC's goal is to make nomenclature standards useful on a broad basis, rather than for just a particular group.

The pharmaceutical industry has told us that they are anxious to use CDER nomenclature standards for all drug submissions, and a number of pharmaceutical firms have already asked for the Data Standards Manual. What are the consequences for CDER if the pharmaceutical industry utilizes our nomenclature standards? The most important one is that reviewers will no longer have to spend time normalizing clinical data from multicenter studies. For instance, when a patient's height is now reported, two medical centers may decide to report data on 78 subjects in centimeters, while three others report their data on 116 subjects in inches. These different measurement systems require a reviewer looking at raw data to first convert each of the inch values to centimeters. Pharmaceutical firms that embrace CDER nomenclature standards would no longer leave this issue to each participating center.

As industry adopts CDER nomenclature standards, we anticipate they will be incorporated into electronic submission forms. This will expedite the migration of data into our databases, since we will bypass the data extraction and data entry steps. Obviously, this raises some concerns about data quality assurance, but we are confident that adequate safeguards can be instituted. Our anticipated result will be streamlined database management.

William A. Hess (e-mail HESS) is the Center's lexicographer.

Nomenclature Committee Seeks Additional Members

If you are interested in representing your office on the NSC, please contact both your information technology focal point and office director. Each office may nominate one member and one alternate to the NSC. Current members are:

- **Ronald Brown,** Office of Management, 443-0500.
- **Brenda Buster,** Office of Management, 827-3276.
- **William Hess,** chairperson, Office of Management, 443-3910.
- **Joan Ginetis,** Office of Review Management, 594-2110.
- **Thomas Hassall,** Office of the Center Director, 594-5412.
- **Charles Hoppes,** Office of Generic Drugs, 594-0365.
- **James Moore,** Office of Epidemiology and Biostatistics, 827-3225.
- **Meade North,** Office of Pharmaceutical Science, 594-0104.
- **Robert Reinwald,** Office of Management, 594-1086.
- **Arthur Shaw,** Office of New Drug Chemistry, 443-0479.
- **Rona Sun,** Office of Management, 443-3910.
- **Kathy Taylor,** Office of Management, 827-3276.
- **Charlotte Yaciw,** Office of New Drug Chemistry, 827-2050.

—William A. Hess

Reviewers Affairs Corner

Communications Links Broaden To Include *Pike*

By Karen Oliver

The Reviewers Affairs Committee (RAC) was established, approximately three years ago, as a communications link between division reviewers and CDER management. Specifically, the RAC is involved in developing recommendations for presentation to the Center director and the management staff (a quarterly event) and providing comment on issues referred to the RAC by CDER management after discussion with division reviewers.

As the last order of new business for 1996, the RAC unanimously voted to initiate a monthly column in *News Along the Pike*. I volunteered to author the articles, since I have an "in" with the editor. After a few sleepless nights on my part, I consulted with **Janet Higgins,** the newly elected RAC chairperson, and we formulated a plan for the kick-off article as well as follow-up *Pike* articles. This month, we take a look down memory lane, highlighting 1996. In the February *Pike*, we will publish RAC's 1997 representatives, alternates and subcommittee membership.

Two representatives from each review division are elected by you, the reviewers, to represent you, the reviewers, at the RAC meetings. The RAC holds its business meetings on the second Tuesday of every month from 1:30 to 3 p.m. The minutes of the meetings are available for your viewing pleasure on the X:drive in the folder Coorcomm\Rac\Minutes. Check them out. Print them. Read them. Share them.

Many guest speakers presented timely information on topics of interest to the RAC including: new reviewer's orientation; funding for intramural research; CDER Honor Awards Program; CDER MAPPs; the World Wide Web (Internet and intranet); an overview of last year's organization assessment; and the Master Regulatory Science Reviewer Project.

Highlights from the subcommittees and task forces include:

- **Comparable Pay Subcommittee.** Drafting position descriptions for the "master reviewer" concept and the status of Phase II implementation of Title 38.
- **Operational Procedure Subcommittee.** Preparing a notebook for RAC representatives that would give them basic information about the RAC. The notebooks will be distributed to the RAC members this month.
- **Subcommittee for Preparation of the Reviewers Handbook.** Expanding and editing the contents of the draft CDER Reviewers' Handbook.
- **Training and Communications Subcommittee.** Evaluating the MAPPs.
- **Networking Subcommittee.** Sponsoring last year's reviewer's social held in March.
- **CDER Honor Awards Task Force.** Drafting recommendations for the CDER Honor Awards program and presenting the recommendations to CDER's Office of Management for further review and action.
- **Task Force for Survey of Reviewers.** Developing a survey instrument to be distributed in 1997.
- **By-Laws Revision Subcommittee.** Amending the committee's by-laws.

We look forward to hearing your kudos, constructive criticisms, questions or comments (e-mail OLIVERK).

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

Kessler Calls Record 53 NMEs in 1996 a Symbol of Hope

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double the pace it had sustained during the first half of the 1990s. During his speech, Kessler put that achievement in historical perspective.

"Let's go back to the passage of the Kefauver-Harris amendments in 1962," he said, "and review the number of new molecular entities that have come on the market each year. The average number of NMEs in the 1960s was 13.7. In the 1970s, that went up to 17.3. In the 1980s, the average was 21.7, and in the first half of this decade, the average is 25.6."

Kessler pointed out that records in approvals and review times are more than mere numbers."What is important is that those numbers are attached to specific therapies," he said. "It has been an unprecedented year for new therapies, highlighted by the historic efforts of a handful of pharmaceutical firms to develop the protease inhibitors that are used to treat AIDS. It is an amazing achievement. The companies involved in developing the protease inhibitors: Abbott's team led by **Andre Pernet;** Roche's team led by **Wajen Suh;** Merck's team led by **Ed Scholnick;** Agruron's team led by **Barry Quart,** and FDA's team led by **David Feigal** including **Jeff Murray, Stanka Kukuich, Rachel Berman, Steve Gitterman, Paul Lu, Chi-wan Chen** and many others deserve special recognition and our gratitude in getting those protease inhibitors to patients in record time."

Kessler attributed the success of 1996 not only to streamlining efforts at the Agency but also to "the scientific seeds that were sown years ago."

The full text of Kessler's remarks can be found on the FDA's Web site at:

http://www.fda.gov/opacom/kessler.html

Slides from the speech are available by following the links on FDLI's Web site at:

http://www.fdli.org

EEO Corner

Advisory Council To Focus On Common Issues

By Gloria Marquez Sundaresan and Margaret Bell

The Center's 1997 EEO Advisory Council will focus its efforts on finding positive ways to address issues developed during open forums for the Center's minority employees held during the last year and a half. These open forums were conducted for Asian Pacific Americans in August 1995, for African Americans in February 1996 and for Hispanics in March 1996. Examples of common issues from the first forum include underrepresentation of women and minorities at the GS-14 level and above, glass ceiling, training, career development, awards and promotions.

The Asian Pacific American (APA) open forum was sponsored by the CDER EEO office and was attended by Asian Pacific Americans from all FDA centers in the Rockville area. **Linda Suydam,** who was at that time Interim Deputy Commissioner for Operations and **Cecilia Maxwell,** Special Assistant to the Commissioner, were at the meeting.

February is Black History Month, established by Dr. Carter Godwin Woodson, known as the Father of Black History and the founder and director of the Association for the Study of Negro Life and History. It began in 1926 as Negro History Week and was expanded in 1976 to a month designed to commemorate the contributions to this country made by African Americans.

African Americans came from a civilization older than recorded history, and many arrived in this country with its early European explorers, including Columbus and De Soto. They have been an integral part of American history ever since and have enriched us all with contributions in every field: business, literature, politics, the arts, athletics, medicine, education and religion.

Although African Americans have been active in the development of the United States, along with other races and nationalities, in many cases, their contributions have been ignored or misrepresented. Black History Month is designed to focus on these contributions.

Gloria Marquez Sundaresan and Margaret Bell are members of the Center's EEO Staff.

CDER's EEO Staff Plans Educational, Cultural Calendar

By Margaret Bell and Diane Smith

Mark your calendars for CDER EEO special observances and dates:

February (Black History Month)**:**
- The theme is African Americans and Civil Rights–A Reappraisal. The FDA program on Feb. 19 will feature the Duke Ellington School of the Arts.

March (Women's History Month)**:**
- An exhibit opens on March 1, and the FDA program on March 20 is Issues in Women's Health.

April:
- CDER's Diversity Day food fest, Parklawn, Conference Rooms D and E, April 8.
- Symposium on Career Opportunities in Biomedical Public Health Science (CDER Workshop), TBA.
- Secretaries' Day observance, April 23.

May (Asian Pacific American Heritage Month)**:**
- Federal Asian Pacific American Council Training Conference, Doubletree Hotel in Rockville, May 5 to 7.
- Congressional Asian Pacific American Caucus Institute Legislative Conference in Washington, May 6.
- National Asian Pacific American Women (NAPAW), TBA.
- CDER Awards Ceremony, including the EEO Achievement Award, May 9.
- National Image Training Conference, Denver, TBA..

June:
- President's Committee on Employees with Disabilities Conference, Washington Hilton, June 4 to 6.
- Brown Bag Seminar–Career Assessment, June 12.

July:
- Federally Employed Women's (FEW) Training Conference, Dallas, July 9 to 12.
- CDER Workshop at FEW, July 9 and 10.
- National La Raza Training Conference, Chicago, July 20 to 24.

August:
- Blacks in Government (BIG) Training Conference, Washington, Aug. 18 to 22.
- CDER Workshop at BIG, TBA.
- Women's Equality Day; (CDER activity TBA), Aug. 25.

September (Hispanic Heritage Month):
- CDER and FDA observances, Sept. 15 to Oct. 15.
- **October** (Disability Awareness Month):.
- CDER and FDA observances TBA..

November (Native American Heritage Month):
- CDER EEO activity, Nov. 1.

December:
- Perspective on Employment for People with Disabilities Training Conference, Washington, TBA..

January 1997:
- Martin Luther King, Jr., commemorative program, TBA..

Margaret Bell and Diane Smith are members of the Center's EEO Staff.

CDER Takes Lead in Dumping Time Clocks, Sign-In Sheets

By Linda Brophy and Russ Abbott

Starting Jan. 19, if you are a CDER civilian employee, you are no longer required to use time clocks or sign-in and sign-out sheets. This is an early move by the Center to implement one part of Secretary of Health and Human Services Donna Shalala's family friendly workplace initiative. The Center has delegated to the major offices the details of the new policy. They, in turn, are likely to delegate further to sub-offices, and divisions.

Key to successful conversion will be your self-certification of the hours you worked. There are several ways in which you may have been asked to do this and account for how much credit time, overtime or compensatory time you earned, and how much leave, credit time or compensatory time you used. Examples of some of the more common options offered to you may include:

- Keeping a written log of your daily hours. These will be summarized and you may be asked to e-mail them or give a signed copy to your timekeeper.
- Reporting by exception. Your timekeeper and supervisor will assume you work your normal tour of duty and a regular 80 hours a pay period unless you report a variation, such as taking leave or earning credit hours.
- Using another method agreed upon by you, your timekeeper and your supervisor.

Timekeepers will no longer be responsible for calculating how many hours you worked and how many credit hours you earned. You will have to do this yourself. Your certification is a legal document and will become part of the official time and leave record.

Leave rules, regulations and policies in place at your workplace remain the same. The rules for obtaining approval for annual leave and sick leave and for earning and using credit time, compensatory time and overtime also remain unchanged. As before, you will need advance approval to work overtime. Your timekeeper will keep track of and tell you how to report special leave categories such as family leave, leave for adoption or bone marrow donation.

Russ Abbott is Director of the Office of Management and Linda Brophy is Associate Director of the Office of Training and Communications.

Reviewer's Corner

Pursuit of New Learning Calls for Personal Balancing Act

By Lydia Kaus

In caps and gowns, students leave the stage amid a roar of applause. Most of us can remember that turning point in our lives. It was the beginning of a new direction–for most of us the launch of a new career. It was a turning point, not the end of seeking new knowledge and not the end of learning. Education gave us the tools to learn, to imbibe new thoughts, to approach ideas, to be able to apply knowledge creatively and to pass it on to others.

In the changing climate of regulatory science, we are facing increased demands for accountability, particularly in the expenditure of our time. The demands on the time we devote to professional learning are different for each of us according to our own experience. Someone new to regulatory science and its procedures focuses on applying his or her current knowledge and learning about regulations. The very "newness" of the position instills an enthusiasm for the task at hand.

For the more seasoned regulatory scientist, there is a pressing need to continue to be self-motivated, to maintain the enthusiasm for learning and new ideas. Sometimes amid the routines of our daily work, we may lose the self-motivation to continue to develop new skills and to strive to keep in step with the latest scientific and medical knowledge. However, it is in developing new skills and knowledge that we can inject creativity into our work, imparting a new clarity and aspect to a review.

We need to find a personal balance between acquiring new skills and keeping abreast of scientific or medical knowledge. Emphasis on computer or managerial skills over regulatory science could result in an efficient but stagnant environment. Emphasis on regulatory science but lack of managerial or organizational skills could result in an intellectual morass.

The experienced reviewer can be in the unique position of being familiar with regulatory science and classical drug development. This reviewer will have a skill of application and have developed a technique of understanding of what can be successfully applied. As new knowledge becomes available, the challenge is to extend this skill of application and to develop an ability to sense what new ideas can result in success.

Success can be thought of in different ways: a review that is more succinct and pertinent or important and relevant data obtained during the drug development process as a result of active input from the Agency. Success could be data that subsequently becomes relevant when applied to another indication or a new patient population.

We cannot lose from pursuing knowledge. We gain from self-development, adapting to change and being challenged in our reviews and challenging others to apply information to their drug products. We are in a unique position to be able to know what is considered state-of-the-art from the information being submitted, to set the standard for others and to pass on "creative" regulatory science to others. Our responsibility is to help forge an efficient and creative environment in which there is a sense of energy and a high standard of public service.

Lydia Kaus is a pharmacokinetic reviewer and team leader with the Division of Pharmaceutical Evaluation II.

FDA Proposes to Withdraw Seldane Approval

(Continued from page 1)

that terfenadine-containing products should be removed from the market. Manufacturers of these products have 30 days from publication of the Jan. 14 notice to request a hearing to show why approval of terfenadine should not be withdrawn.

Patients currently taking terfenadine products should talk to their doctors about switching to alternative medications. To help the Agency's staff members who respond to consumers, health professionals and the media, the Center's Office of Training and Communications coordinated a briefing the Friday before the *Federal Register* notice went public. The briefing was for the FDA's Office of External Affairs, the MedWatch staff and public affairs specialists in the FDA field offices who heard the briefing by teleconference. **John Jenkins, M.D.,** Director of the Division of Pulmonary Drug Products, conducted the briefing. On the following Monday, **Robert Temple, M.D.,** Associate Director for Medical Policy, briefed key external health professional organizations.

These outreach programs, the first of their kind, were led by OTCOM's Director, **Lucy Rose. Patricia DeSantis,** Office of Review Management, and OTCOM's **Marcia Trenter** and **Angela Youngblood** were instrumental in coordinating participants and logistics. Representatives from the field and Office of External Affairs were enthusiastic for this type of comprehensive briefing on a high-interest issue prior to public announcement. "This is the type of communication initiative that will make a difference in how well prepared our Center and Agency are to educate our constituencies," Rose said.

In the supplementary information to the *Federal Register* notice, Center officials outlined a five-stage reasoning process that led to their decision to take steps to withdraw terfenadine from the U.S. market:

- Prior to the approval of fexofenadine, terfenadine provided a unique therapeutic alternative for which the associated risks were acceptable.
- Terfenadine provides no therapeutic benefit to any patient population that is not also provided by fexofenadine, because fexofenadine is identical in molecular structure to terfenadine's therapeutically active metabolite.
- Current data demonstrate that fexofenadine lacks the serious cardiovascular risks associated with the misuse of terfenadine. Approximately five months of marketing experience with fexofenadine in the United States have not resulted in any reports of serious cardiac arrhythmias.
- Despite the many interventions undertaken by the Agency and by the drug sponsor (three "Dear Doctor" letters, labeling changes and educational campaigns), Center officials concluded that coprescribing, codispensing, and concomitant use of terfenadine with a growing list of medications that inhibit its metabolism continues and could not be expected to be completely eliminated.
- Consequently, the officials concluded, terfenadine, cannot be considered safe under the conditions that formed the basis upon which FDA initially approved the application.

People Along the Pike

Center, FDA Authors Debunk Myth of 'Drug Lag' in *JAMA*

Top Agency and Center officials teamed up in the Dec. 11 issue of the *Journal of the American Medical Association* to debunk the issue of "drug lag" in special communication article titled: "Approval of New Drugs in the United States: Comparison With the United Kingdom, Germany, and Japan." **Murray Lumpkin, M.D.,** Deputy Center Director for Review Management, and **Robert Temple, M.D.,** Associate Center Director for Medical Policy, share authorship with FDA Commissioner **David A. Kessler, M.D., J.D., Arthur E. Hass, Jr.,** from the Agency's Office of Planning and Evaluation, and **Karyn L. Feiden.**

The authors investigated the marketing approval dates of 214 drugs newly introduced into the work market in the five-year period 1990-94. Their analysis shows that the United States and the United Kingdom have similar patterns of drug availability. U.S. citizens have a number of new drugs with important medical benefits not yet at available to U.K. citizens. The United States outpaces both Germany and Japan in approving important new drugs. The authors point out that making comparisons among countries is complex.

"Every country has an array of drugs available that is different from that of other countries," they write in conclusion. "Therapeutic practices, pricing and reimbursement structures, industry marketing strategies, and cultural mores are just a few of the elements that may affect drug availability, regardless of the nature of the regulatory system in place. Nonetheless, Americans have early access to numerous therapies with significant public health benefits and are missing very few drugs that are novel or medically important."

For help pulling the article together, the authors acknowledged the assistance of **James O'Hara, Stuart L. Nightingale, M.D., Paul L. Coppinger, John P. Lucas, Sc.D.,** and **Julia L. Ho** from the Agency and, from CDER, **Stella G. Machado, Ph.D., Jonathan Levine, M.A., Charles Anello, Sc.D., Yo Tsong, Ph.D.,** and **Donald Aronson.**