news along the pike

FEBRUARY 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

VOLUME 7, ISSUE 2

INSIDE . . .

PIKE'S CORNERS . . .

Center's Senior Management Looks at Path Forward

Quality Decision-Making, Risk Management ID'd as Priorities

BY JANET WOODCOCK, M.D.

Throughout CDER, we have been working to implement the plans laid out by the Center during 1995 and 1996 in our planning process as well as the mandates in the 1997 FDA Modernization Act. It has taken tremendous effort by many people to respond to all the tasks. However, much of this work is now completed or well under way.

It is now time to step back, take stock and determine our path forward. As a first step, CDER reconstituted its Senior Management Team consisting of those who report directly to me. The team met Jan. 16 to 18 to discuss strategic planning for the Center. The members of the SMT will be discussing the results of this meeting within their offices in the upcoming weeks, so there should be plenty of opportunities for you to comment.

The SMT meeting started out with office directors reviewing the status of programs in their areas. Both the strength and breadth of our activities are impressive. We have positive achievements in many areas, from our award-winning training program to the most productive regulatory policy shop in the Agency. We are also generally working well in cross-programmatic areas. We are well regarded throughout the Agency for excellent science, strong policy development and good management.

The SMT next discussed the most serious problems facing the Center and how they should be prioritized. The team identified two priority issues for the Center.

(Continued on page 8)

Thompson Takes Helm at Health and Human Services

Newly sworn-in Health and Human Services Secretary **Tommy G. Thompson** addressed a gathering of HHS staff on Feb. 2. About 1,000 employees crowded in the Great Hall of the Hubert H. Humphrey Building to hear Thompson, while others watched by videoconference and on the Internet.

Thompson, who stepped down as longest-serving governor in Wisconsin history and longest-serving current U.S. governor, is the 19th person to hold the Cabinet-level office heading the department, which, prior to 1980, was the Department of Health, Education and Welfare.

"I took this job because there is no other job in America where you have a greater opportu-

(Continued on page 8)

3rd Abrams Lecture to Focus on Pediatric Drug Development

The complexities as well as the impact of science, technology and medicine on pediatric drug development will be highlighted during the Center's third William Abrams Lecture.

The lecture, cosponsored by the American Society for Clinical Pharmacology and Therapeutics, is scheduled for March 14 at 1:30 p.m. in the Building 1 auditorium of the University of Maryland's Shady Grove campus.

The Abrams lecture will be delivered by Stephen P. Spielberg, M.D., Ph.D. His topic is: "Drug Development and Therapeutics: What Our Children Have Taught Us."

Dr. Spielberg is vice president of pediatric drug development at the Janssen Research Foundation in Titusville, N.J.

He is the recipient of the 1992 Rawls-Palmer Award and Lectureship from the American Society of Clinical Pharmacology and Therapeutics and the first recipient of the Werner Kalow Award in Pharmacogenetics and Drug Safety presented in 1995.

The lecture series is named for William Abrams, M.D., who died in 1999. Dr. Abrams, the widely respected executive director for scientific development at Merck & Co. Inc, was instrumental in establishing the Center's Staff College, the forerunner of the Division of Training and Development.

JOE'S NOTEBOOK

HHS Historical Highlights

This month, with a new HHS secretary at the helm, you may enjoy reading a review of the department's highlights. HHS traces its origins to the earliest days of the nation. Important federal actions before the department was created include:

- *1798.* The first Marine Hospital, a forerunner of today's Public Health Service, is established to care for seafarers.
- *1862.* President Lincoln appoints a chemist, Charles M. Wetherill, to serve in the new Department of Agriculture. This marks the beginning of the Bureau of Chemistry, FDA's forerunner.
- *1887.* The federal government opens a one-room laboratory on Staten Island for research on disease, planting the seed that grows into the National Institutes of Health.
- *1906.* Congress passes the first Food and Drug Act, authorizing the government to monitor the purity of foods and the safety of medicines, now an FDA responsibility.
- *1935.* Congress passes the Social Security Act.
- *1946.* The Communicable Disease Center is established, forerunner of the Centers for Disease Control and Prevention.

On April 11, 1953, the Cabinet-level Department of Health, Education and Welfare, officially came into existence. A 1979 law established the Department of Education as a separate department. HEW officially became the Department of Health and Human Services on May 4, 1980. Some highlights of the combined HEW and HHS history include:

- *1955.* The Salk polio vaccine is licensed.
- *1961.* First White House Conference on Aging.
- *1964.* Surgeon General's Report on Smoking and Health.
- *1965.* Medicare, Medicaid and Head Start programs begin.
- *1966.* International Smallpox Eradication program, led by PHS, begins. Worldwide eradication of smallpox accomplished in 1977.
- *1971.* National Cancer Act.
- *1977.* The Health Care Financing Administration begins managing Medicare and Medicaid separately from the Social Security Administration.
- *1980.* Federal funds become available to states for foster care and adoption assistance.
- *1981.* AIDS, the acquired immune deficiency syndrome, is identified.
- *1984.* PHS and French scientists identify the HIV virus.
- *1984.* National Organ Transplantation Act.
- *1985.* A blood test to detect HIV is licensed.
- *1989.* Agency for Health Care Policy and Research.
- *1990.* Human Genome Project; the Nutrition Labeling and Education Act; Ryan White Comprehensive AIDS Resource Emergency Act.
- *1995.* Social Security Administration becomes an independent agency.
- *1999.* AIDS drops from the top 15 causes of death.
- *2000.* Scientists complete the map of the human genome.

You can find more HHS historic highlights at http://www.hhs.gov/about/hhshist.html. You can also explore an illustrated history of CDER on the Center's Web site at http://www.fda.gov/cder/about/history/.

Credit: The *Pike* ran out of room for author credits to the bioavailability and bioequivalence article on pages 5 and 6. **Mei-Ling Chen** is associate OPS director for quality improvement, BA/BE, and a topic leader on the Biopharmaceutics Coordinating Committee. **Larry Lesko** is director and **Dale Conner** is a supervisory chemist in the Office Clinical Pharmacology and Biopharmaceutics. Larry and Dale are co-chairs of BCC.

news along the pike

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http://www.fda.gov/cder/pike.htm
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Have ideas, news or comments to contribute?
Please contact a member of the Editorial Board or:

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CDER Office of Training and Communications (HFD-200)
Parklawn Building, Room 12B-45

Editor: Norman "Joe" Oliver (OLIVERN)
Associate Editor: Patrick Clarke
Phone: (301) 827-1670
Fax: (301) 827-3055

OMBUDSMAN'S CORNER

The Art of Reading Tea Leaves

BY JIM MORRISON

As I've noted many times, those outside CDER often view our new drug review process as a giant black box. In the absence of complete transparency, applicants sometimes look for occult signs and surrogate markers to tell them how their new drug applications are progressing.

Applicants who are not seasoned veterans at maneuvering NDAs through the review process sometimes interpret the statements from Center staff and Agency actions in a manner that is just about as accurate as reading tea leaves.

Lately it seems that I've been seeing more unsuccessful tea-leaf reading than usual. I thought it would be useful to those on both sides of the regulatory fence to share some examples I've encountered.

These examples all relate to firms that have come to me in a state of shock after they received not approvable letters. I've divided them into erroneous interpretations of statements made by CDER staff and false inferences based on activities by the Agency during the review process.

Statements

In meetings or telephone conversations with CDER reviewers and project managers, applicants may ask: "Do you need any more information?"

The reviewers may say: "No, we have all the data we need," or, "No, there are no outstanding issues." They mean that the application is complete—not necessarily approvable—and that no more amendments to the NDA are needed for them to reach a decision.

Unfortunately, some applicants think this means that there are no problems with the drug, the data or the application.

As a word of advice to reviewers and project managers, it would be good to emphasize to applicants that we won't know whether the application is approvable until all the data have been reviewed.

Another occasionally misunderstood statement is, "There are no issues that need to go to the advisory committee."

Some applicants take this to mean that the data are so good that the drug is clearly safe and effective. But it could also mean that the data are so negative that the drug is clearly unsafe or ineffective, so there is no reason to waste the advisory committee's time. Most often it means that the drug is not novel, and there are no real areas of uncertainty.

Sometimes applicants interpret the absence of contacts or questions to mean everything is fine with the application. "No news is good news" may apply when your teen-ager borrows the car, but it is useless in predicting the outcome of an NDA review.

Activities

I have heard applicants say, "But DSI [the Division of Scientific Investigations, which inspects clinical investigators] did their inspection, and everything seemed fine. They wouldn't have done the inspection if the application was not approvable." Wrong.

I've also heard the same thing said about field investigators inspecting the manufacturing facility for current good manufacturing practices.

Those assumptions may have had some validity years ago. However, with the short user-fee review timeframes in place today, inspections are ordered very early in the review process, before any conclusions can be made about whether the application is approvable.

Even if the reviewing division believes that an application will not be approvable, the inspections are done so all deficiencies can be identified and conveyed to the applicant.

The Center gets many applications from startup companies run by entrepreneurs who have invested years of sweat and a lot of their own money in the development of a single product that will make or break them. It is only natural that they are extremely anxious about the progress of their application. They seek any clue they can find about how their drug is faring.

With that in mind, it is important for us to be very careful to avoid inadvertently misleading applicants by being less than crystal clear about what our statements and activities mean with respect to the outcome of their applications.

Jim Morrison is the Center's ombudsman.

PIKE'S PUZZLER

Check Your Units

BY TONY CHITE

1. A unit of linear measure that is the equivalent of 2.54 centimeters is:

a. 5.08 millimeters
b. 1 inch
c. 2540 microns
d. 0.254 yard

2. A unit of electric power that is the work done at the rate of 1 joule per second is:

a. 1 watt
b. 1 amp
c. 1 volt
d. 1 erg

3. A unit of whole blood is:

a. 1 quart
b. 30 milliliters
c. 450 milliliters
d. 100 milliliters

4. A unit of force that when acting upon a mass of 1 gram will impart to it an acceleration of 1 centimeter per second per second, is:

a. 1 erg
b. 1 joule
c. 1 British thermal unit
d. 1 dyne

5. A unit of heat required to raise the temperature of 1 kilogram of water 1 degree Celsius at a specified temperature is a:

a. Fahrenheit
b. calorie
c. kelvin
d. BTU

6. A unit of power in the U.S. customary system equal to 745.7 watts or 33,000 foot pounds per minute is:

a. 1 horsepower
b. 1 revolution per minute
c. 1 erg
d. 1 Fulton

Key: 1b; 2a; 3c; 4d; 5b; 6a

Tony Chite is a pharmacist and CSO in CDER's DFOI.

How to Copy Tables from PDF to Word; Outlook Rollout Update

Q: There is a table in a PDF file that I would like to copy and paste into a Word document so I can change the data. How is this done?

A: The same tool that is used to copy formatted text is also used to copy and paste tables from PDF to other applications. Tables copied from PDF maintain the original format of the table, preserving the data as rows and columns of cells.

To copy and paste a table:

- On the tool bar in Acrobat, click on the Text Select Tool. 
- Drag the mouse to the right and select the Table|Formatted Text Select Tool. 
- Click and drag a box around the table.
- Make sure the type is Table. If not, right-click in the table and choose Table from the popup menu.
- On the menu bar, select Edit|Copy.
- Go to your Word document.
- On the Word menu bar, select Edit|Paste or click the paste button on the toolbar.

Note: Additional cells may be created when the table is pasted, especially if the PDF table has more than one line in a cell. Follow the directions below to merge the extra cells and recreate the PDF table:

- Select the table.
- Click the borders button on the Formatting toolbar to restore borders. 
- Use the eraser tool or the merge cells tool to remove the excess borders. 

Refer to the Adobe Acrobat Help menu for additional PDF tips. Also, contact the Help Desk (HELP) for additional Acrobat and Word questions.

Outlook Rollout Continues

The Outlook e-mail rollout is continuing. So far, the installation has been completed at CDER sites at Corporate Boulevard, Metropark North 1 and 2 and 8301 Muirkirk Rd. We anticipate completing the rollout to all Center locations by the end of 2001.

The migration will proceed in a series of steps. First, an OIT technician will install Outlook on your PC, which will take between 15 and 45 minutes. You will not need to be present during the installation. At this point, you will continue to use TeamLinks/ALL-IN-1 for e-mail.

The next step is training and installation of Outlook on your government home PC. You will be notified by someone in your division (usually an IT focal point or secretary) regarding dates and times for Outlook training and procedures for government home PC setup.

> The same tool that is used to copy formatted text is also used to copy and paste tables from PDF to other applications. However, additional cells may be created when there is more than one line in a cell

In training you will learn the basics of Outlook and CDER specifics. Once you have completed training, you will be switched from TeamLinks/ALL-IN-1 to Outlook by 3 p.m. the following business day. Your new e-mail messages will go to Outlook, and you will use Outlook to read and compose e-mail messages.

You will still be able to use TeamLinks/ALL-IN-1 to view old e-mail messages. For more information concerning remote access and home use, see the OIT intranet site at http://oitweb/Software/MSOutlook-2000/default.htm.

Finally, just a reminder on one key difference between Outlook and TeamLinks/ALL-IN-1: Outlook is not a substitute for a file storage system. Each user has a quota of 70 megabytes. While this is large enough to accommodate e-mail, it is not large enough to serve as a repository for attachments that arrive via e-mail.

Now is a good time to get in the habit of managing your e-mail. Helpful actions include deleting messages that you do not need, periodically checking and cleaning out e-mail folders and breaking the habit of using e-mail for file storage. By including these small changes into your daily routine, you will help insure a smooth transition to Outlook.

Go to our intranet site http://oitweb and follow the link from the Notices section or contact the Help Desk (HELP) with any e-mail questions.

March IT Training*

Monday	Tuesday	Wednesday	Thursday
			1 **E-Doc/ RetrievalWare (C)** 9:00-12:00 **E-Doc/ RetrievalWare (C)** 1:00-4:00
5	6	7	8
12 **E-Doc/ RetrievalWare (C)** 9:00-12:00 **E-Doc/ RetrievalWare (C)** 1:00-4:00	13 **Word Intro (C)** 9:00-12:00 **E-Doc/ RetrievalWare (P)** 9:00-12:00 **Word Formatting (C)** 1:00-4:00	14 **Word Tables (C)** 9:00-12:00 **Excel Intro (P)** 9:00-12:00 **DFS (C)** 1:00-4:00	15 **PowerPoint Intro (C)** 9:00-12:00 **PowerPoint Charts (C)** 1:00-4:00
19 **E-Doc/ RetrievalWare (P)** 9:00-12:00 **E-Doc/ RetrievalWare (P)** 1:00-4:00	20	21 **DFS (P)** 1:00-4:00	22 **PEDS (C)** 9:00-12:00 **NEST (P)** 9:00-12:00 **NEDAT (P)** 1:00-4:00
26 **E-Doc/ RetrievalWare (C)** 9:00-12:00 **E-Doc/ RetrievalWare (C)** 1:00-4:00	27	28 **DataMart (C)** 1:00-4:00	

Key: Corporate Boulevard (C), Park Building (P)

*There are no classes scheduled for Fridays in March.

The catalog, training materials, schedule and on-line registration can be found under Training at http://oitweb/.

PEDIATRICS CORNER

Newly Approved Changes Address Scientific Knowledge Gaps

BY DIANNE MURPHY, M.D., ROSEMARY ROBERTS, M.D., WILLIAM RODRIGUEZ, M.D., AND TERRIE CRESCENZI, R.PH.

In last month's *Pike,* we reported that the pediatric exclusivity provision of the 1997 FDA Modernization Act is generating many clinical studies and useful prescribing information.

Most of the 16 products with labeling changes approved so far have shown significant findings. The full list is on CDER's pediatric Web site at http://www.fda.gov/cder/pediatric/labelchange.htm.

The effort to improve pediatric labeling is exposing scientific knowledge gaps. An evolving trend is that there is a real difference in how children handle the drugs. Children under 5 may metabolize a drug more quickly.

Overall, important new information has been uncovered that will help pediatricians and other doctors prescribe medication with confidence. For example, ibuprofen, used to treat fever, minor aches and pains and cold symptoms, now has an approved over-the-counter use in children as young as 6 months.

Five drugs have new information related to dosing:

- Etodolac, a new therapy for juvenile rheumatoid arthritis for children 6 to 16 years old, has been proved safe and effective. Younger children need a higher dose (on a per kilogram basis) that is about two times the lower dose recommended for adults.
- A new oral liquid formulation of midazolam, used to treat anxiety prior to procedures or surgery, needs to be started at the lower end of the dosing range for a subpopulation at higher risk for adverse events—children with congenital heart disease and pulmonary hyper-tension--to avoid serious respiratory complications.
- Fluvoxamine, used to treat obsessive compulsive disorder, may require an increased dose in adolescents up to the adult maximum dose, whereas girls 8 to 11 years demonstrated a much higher exposure to the drug and therefore lower doses may produce a therapeutic benefit.
- Gabapentin, used in treating epilepsy, is cleared more rapidly in children under 5; and they require higher doses in order to have effective control of their seizures. Also, unique pediatric neuropsychiatric adverse events such as hostility, including aggressive behavior, may occur.
- Loratadine, a prescription allergy medicine, can be given to children 2 to 5 years old at one-half the dose used for children ages 6 to adolescence.

The authors are CDER's Pediatric Team.

OPS Issues Important Guidance on Bioavailability, Bioequivalence

BY MEI-LING CHEN, PH.D., LAWRENCE LESKO, PH.D., AND DALE CONNER, PHARM.D.

The Center's Office of Pharmaceutical Science has recently published a guidance that contains the latest scientific thinking on bioavailability and bioequivalence.

The guidance, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations,* is on the Internet at http://www.fda.gov/cder/guidance/3615fnl.htm.

The document provides a comprehensive overview of regulatory approaches to measure bioavailability and establish bioequivalence for orally administered drug products. The approaches are also generally applicable to non-orally administered drug products, such as transdermal delivery systems and certain rectal and nasal drug products, where reliance on systemic exposure measures is suitable to document bioavailability and bioequivalence.

The guidance is designed to reduce the need for drug-specific bioavailability and bioequivalence guidances. It replaces a number of previously issued drug-specific bioequivalence guidances. It will also reduce the regulatory burden on sponsors in many cases.

Bioavailability and bioequivalence studies are key regulatory studies for ensuring consistent quality and performance of drug products in the U.S. marketplace.

Bioavailability studies are important components of applications for new drugs. These studies focus on determining the process by which a drug is released from the dosage form and moves to the site of action. Bioavailability can be generally documented by a systemic exposure profile obtained by measuring the concentration of the drug, its metabolite or both in the circulation over time.

In bioequivalence studies, the systemic exposure profile of a test drug product, such as a generic drug, is compared to that of a reference drug product, such as an innovator drug. For two orally administered drug products to be bioequivalent, the active drug ingredient in the test product should exhibit the same rate and extent of absorption as the reference drug product. Bioequivalence studies are key to generic drug applications and for certain manufacturing changes to either innovator or generic drug products that require prior FDA approval.

Many aspects of this guidance represent departures from past practices used to document bioavailability and bioequivalence as the science in this area has evolved. The general intent of these changes is to reduce the regulatory burden on industry, where possible, while maintaining sound scientific principles. Specific examples of these changes include:

- Elimination of multiple-dose bioequivalence studies for modified-release dosage forms.
- Waiver of bioequivalence studies for lower strengths of modified-release dosage forms.
- Waiver of bioequivalence studies for higher strength of immediate-release products.
- Reduced emphasis on measuring metabolites in bioequivalence studies.

There are limits in our ability to assess rate of absorption using most direct and indirect pharmacokinetic measures, including the currently used peak concentration or Cmax. The guidance, therefore, recommends a change in focus from measures of absorption rate to measures of peak and systemic exposure.

Exposure measures are defined relative to early, peak and total portions of the

(Continued on page 6)

REVIEW STANDARDS CORNER

RSS Tackles Quality Assurance, GRPs, Risk Management

BY LISA RARICK, M.D.

The newly formed Review Standards Staff is ready to serve you. We are a team of dedicated staff members who are working toward forwarding several Centerwide initiatives. These programs are designed to support and advance the important work you all perform daily.

Two RSS team members come from the previous Quality Assurance Program staff—**Judy McIntyre** (MCINTYREJU, 4-5613) and **Rubynell Jordan, R.N., MPA,** (JORDANR, 4-5616). Judy and Ruby along with the rest of us will continue to champion efforts to apply quality systems to all that CDER is and does. Use of quality systems will help us better recognize our collective strength and understand how to share the Center's wealth of knowledge within and outside of CDER.

Lindsay Cobbs (COBBSL, 4-5610), a project officer, and **Georigann Ienzi** (IENZIG, 4-5418), a secretary, moved with me from the Office of Drug Evaluation II and continue their work in surveying the Center's postmarketing study commitments. We are required by the 1997 FDA Modernization Act to report back to Congress by Oct. 1 on the status of postmarketing commitments, also known as Phase IV commitments. Thanks to everyone who is contributing time and effort toward making the fulfillment of CDER's congressional requirements a reality. We estimate that this effort involves about 900 applications spanning several decades and including about 3,000 commitments.

Lana Pauls, MPH, (PAULSL, 4-5612), is coordinating the Center's efforts in the area of risk management. She recently worked in coordinating the February workshop on drug-induced liver injury (January *Pike).* Lana comes from the Division of Reproductive and Urologic Drug Products where she served as chief, project management, and associate director.

Michael Ortwerth, Ph.D, (ORTWERTHM, 4-5614), who brings the perspective of his previous responsibilities as a primary chemistry reviewer in the Division of New Drug Chemistry II, will be heading up the coordination and implementation of good review practices. He also brings his very relevant background and interest in quality system principles to the team.

Susan Johnson, Pharm.D, Ph.D., (JOHNSONSU, 4-5415) is our member with a decade of primary clinical review experience with the Division of Pulmonary and Allergy Drug Products who also brings a special expertise in organizational development and a unique approach and passion for CDER learning.

The RSS had the privilege of participating in a two-day planning retreat in January. Here, with facilitation from the Division of Training and Development, we developed the beginnings of our mission and vision philosophies. The center director met with us during our retreat and expressed her strong belief in CDER's work and the need to further maximize quality, accountability and innovation.

We are now staffed and ready to hear from you. We hope to serve as a true "hearing house" for the many excellent ideas you have. We look forward to helping you find ways to proceed and progress. Please contact any of us with your thoughts about our areas. For general questions, contact Georigann or me (RARICK, 4-5412).

Don't be surprised to see us as we seek your help—and we hope to support you—in areas such as GRPs, risk management, quality assurance and change implementation. We ask for your help in suggesting other areas where you would recommend development and support. We are dedicated to applying quality system principles to our own activities. We hope to use future *News Along the Pike* articles and other communication venues to provide reports on our activities.

Lisa Rarick is RSS director.

Guidance Seeks to Reduce Regulatory Burden, Maintain Sound Science

(Continued from page 5)

plasma concentration-time profile after administration of a drug. The change in emphasis allows continued use of Cmax and area under the curve (AUC) as bioavailability and bioequivalence measures. These two measures have been used reliably for regulatory assessment and are useful indicators for safety and efficacy of a drug product. A third measure termed early exposure is recommended for immediate-release dosage forms in some cases.

Another significant change is the recommendation of replicated crossover designs for bioequivalence studies of modified-release dosage forms and highly variable drug products. The rationale is to allow comparison of within-subject variances between formulations and to assess the magnitude of a subject-by-formulation interaction, if it exists.

In general, use of a replicate design reduces the number of subjects needed in a bioequivalence study compared to a non-replicated design. The guidance follows the recommendation of the Advisory Committee of Pharmaceutical Science for continued use of an average criterion for bioequivalence determination with the option of choosing other criteria in compelling circumstances.

To provide statistical criteria and methods for analysis of bioequivalence data, a companion guidance, *Statistical Approaches to Establishing Bioequivalence,* was issued early this year. It is available at http://www.fda.gov/cder/guidance/3616fnl.htm.

In addition to the average approach, the statistical guidance provides two new approaches, termed "population" and "individual" bioequivalence. The population and individual bioequivalence approaches include comparisons of both averages and variances. These new approaches may be useful in some cases for analyzing *in vitro* and *in vivo* bioequivalence studies although we need to gain more experience with the methodology.

Both guidances have been prepared by working groups in the Biopharmaceutics Coordinating Committee after several years of intensive discussion and hard work. They represent the most current FDA recommendations for submitting bioavailability and bioequivalence data in new and generic drug applications.

Controlled Substance Staff Seeks Better Integration into Review Process

BY PATRICK E. CLARKE

The review and policy sections of FDA's Controlled Substance Staff were consolidated and relocated from the Office of the Commissioner to the Office of the Center Director last year. The move aims to increase the staff's effectiveness through better integration into the drug review process.

The 1970 Controlled Substances Act places drugs that have some abuse or addiction potential on schedules that range from I to V. Schedule I drugs, like heroin, are the most addictive and have no current medical use in the United States.

The Drug Enforcement Administration officially places a drug on a schedule based upon the medical and scientific recommendation of Office of the Assistant Secretary of Health, which consolidates recommendations from the Controlled Substance Staff and other concerned HHS agencies.

Based on previous experiences, FDA officials have concluded that the Agency's recommendations should be based on early data showing potential problems, not after something happens once a drug is on the market.

"We really want to be consulted early when a question arises," said **Deborah B. Leiderman, M.D.,** director of the Controlled Substance Staff. "If a product has abuse liability, we need to know. It's much easier to be useful to a division or a sponsor when we're consulted early.

"Within one to two years we hope to be fully integrated in the review process and have clear guidelines for the abuse/dependency assessment process. We want to make sure we speak with one voice as an agency."

The staff interacts regularly with the DEA, the National Institute for Drug Abuse, the Substance Abuse and Mental Health Services Administration, as well as the international drug control community through the State Department and through FDA's International Affairs Staff.

"The emphasis the Center is placing on risk management has helped our decision making process," said **Michael Klein, Ph.D.,** senior interdisciplinary scientist on the staff. "Risk management programs provide another approach in assuring that the drug is used safely after approval for the indication it was approved and the target population."

The seven-person staff consists of two chemists, a pharmacologist, a medical officer who is a psychiatrist, a project manager, a science policy specialist and an administrative support person.

"We do the public health part, and the DEA does the law and order part," Dr. Leiderman said. "We rely heavily on post-marketing surveillance. Abuse liability and assessment of epidemiological data come to us. We are the locus for the Center and the Agency on those issues."

The group has at least 18 active projects currently. A project can take anywhere from a week to a year to complete. Work on investigational new drugs can take even longer.

"We get two to three petitions for rescheduling a previously scheduled drug a year, plus three to four new drugs that require scheduling. In addition, we get an average of four new consultations a week on particular protocols and INDs," Dr. Leiderman said.

The process of determining whether a drug should be scheduled can be quite complex. One of the most difficult scenarios for the staff is scheduling a previously uncontrolled drug, according to Dr. Klein.

Speaking from first-hand experience, he noted that butorphanol tartrate, an opiate-based intravenous anesthetic, had been approved in 1978 as an injectable for pain. But, it had limited distribution because only doctors and nurses could administer it.

"In 1991, the drug company wanted to introduce a new dosage form, as a nasal spray, which opened it up to direct patient use," Dr. Klein said.

At the time, Dr. Klein was a team leader in the review division and had concerns about approving this usage.

"But, the company argued that it was on the market since 1978 with no real abuse noted, which is a very persuasive argument. So, an advisory committee recommended that it go out non-controlled. Within six months we had lots of reports of abuse and overdose," Dr. Klein said.

Ultimately, the drug was placed on Schedule IV, which includes drugs like diazepam.

The need for early consultations with the Controlled Substance Staff if a product has abuse liability cannot be emphasized strongly enough, Dr. Leiderman said.

"One of our goals is to increase our visibility within CDER so all divisions are aware of our purpose. Another is to revise and finalize our Manual of Policies and Procedures for abuse liability consultations," Dr. Leiderman said.

More information on the Controlled Substances Act and the scheduling of drugs can be found on DEA's Web site at http://www.dea.gov/concern/abuse/chap1/contents.htm.

Patrick Clarke is a public affairs specialist in OTCOM.

EEO Corner: Conference Information, Dates, Locations Available

BY GLORIA MARQUEZ SUNDARESAN

The following information on conferences through September is available:

- Federal Asian Pacific American Council, Arlington, Va., May 7-10, 202-782-7335.
- Asian Pacific American Institute for Congressional Studies, Washington, May 10-11, 202-296-9200.
- National Image Inc., Atlantic City, N.J., May 21-26, 303-534-6534.
- League of United Latin American Citizens, Phoenix, Ariz., June 3-9, 202-408-0060.
- Federally Employed Women, Indianapolis, July 9-13, 202-898-0994.
- National Council of La Raza, Milwaukee, July 14-18, 202-785-1670.
- Blacks in Government, Los Angeles, Aug. 27-31, 202-667-3280.
- Society for the Advancement of Chicanos and Native Americans, Phoenix, Ariz., Sept. 27-30, 831-459-0170.

For more information please call the EEO Staff at 301-594-6645.

The author is on CDER's EEO Staff.

SMT Sees Quality Decision-Making, Risk Management as Priorities

(Continued from page 1)

The first is ensuring that we have the highest quality regulatory decision-making. Although we have made great strides in quality in recent years in timeliness and consistency of decisions, the team felt we need to make additional efforts. Examples discussed included good review practices, better dissemination of information across programs and improvements to the actual decision-making process itself. The team agreed to put together a process to identify the most important steps we can take in this area. Each program will be involved in this effort as it goes forward.

The second priority is to embed the principles of risk management into all our regulatory programs. For example, **David Horowitz,** Office of Compliance Acting Director, explained how strategic enforcement—a results-oriented, risk-based process—can be used to improve the compliance of regulated industries.

The team agreed that risk management is a concept that helps unify our disparate regulatory activities. Given our limited resources, risk-based approaches also help us prioritize our actions by focusing on the most important actions we can take to promote health and prevent harm.

To understand where all our programs are with respect to risk management, the Review Standards Staff (see page 6) will be following up with groups throughout the Center. We will then identify the most important steps that can be taken this year.

The SMT also agreed that addressing our priorities will require more attention to good management and leadership practices in the Center. For example, the team agreed that more attention must be paid to succession planning.

Potential leaders and managers must have the opportunities to take on challenges, and additional mentoring activities need to be developed.

We have to take a more standardized approach to information technology and the way it is supported. **Ralph Lillie,** Office of Information Technology Director, presented OIT's plan for standardizing desktop management, which the team endorsed. It was also agreed that a survey of various operational needs would be undertaken. **Randy Levin, M.D.,** the Center's electronic submissions coordinator for, agreed to do the survey.

We will be engaging people throughout the Center in further planning around the identified issues and goals.

Janet Woodcock is the Center Director.

Thompson Meets with Employees, Outlines "Aggressive Agenda" for HHS

(Continued from page 1)

nity to help people—to actually make a difference in people's lives and improve the quality of life they lead," Thompson said. Photos of the welcome are at http://www.hhs.gov/news/photos/.

Thompson said that he plans to bring an innovative spirit to HHS and its more than 300 programs. "I'm here to persuade you to do things just a little differently on the national level. I believe so passionately that the issues faced by this department are among the most important facing us as a nation. And I believe that we need to find innovative, creative ways to face these challenges," Thompson said.

"We need to reach out to states and local governments. We need to look at successful models and best practices from all over this country, because there are no one-size-fits-all solutions to the challenges we face."

Thompson said that his "aggressive agenda" includes:

- Modernizing Medicare.
- Enacting a Patient's Bill of Rights.
- Acting to provide access to affordable health insurance for the more than 43 million Americans who are uninsured.
- Continuing welfare reform to help those who go to work to "have the opportunity to continue to move up the ladder of economic success."
- Taking action to establish an office of faith-based and community initiatives.
- Improving foster care and adoption programs around the country.
- Taking a leadership role in women's health.
- Supporting biomedical research.
- Continuing vigilant protection of the safety of the nation's food and drug supply.

He also announced that he would move in the first 100 days of his tenure to "launch a national campaign to raise awareness of organ donation."

A copy of Thompson's speech is available at http://www.hhs.gov/news/speech/2001/010202.html. Following his remarks, he answered questions.

Thompson has dedicated his professional life to public service, most recently serving as governor of Wisconsin since 1987.

He gained national attention for his leadership on welfare reform. As governor, he focused on revitalizing Wisconsin's economy, expanded access to health care for low-income people and education. His biography is at http://www.hhs.gov/about/bios/dhhssec.html.

Thompson takes over at one of the federal government's largest departments.

At $429 billion, HHS has the largest budget among Cabinet-level departments, representing 23 percent of all federal outlays. The Department has 63,000 employees. It includes:

- *Medicare,* the nation's largest health insurer, serving 40 million elderly and disabled Americans.
- *Medicaid,* the joint federal-state program providing health care for low-income Americans.
- *National Institutes of Health,* the world's premier biomedical research institution.
- *Food and Drug Administration,* which has responsibility for safety of products representing 25 cents out of every dollar in U.S. consumer spending.
- *Centers for Disease Control and Prevention,* maintaining a nationwide and global public health network.
- *Administration for Children and Families,* working with states to provide services especially to low-income families
- Six other primary agencies providing services to Americans.

A summary of HHS activities is at http://www.hhs.gov/about/profile.html.