news along the pike

APRIL-MAY 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

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INSIDE . . .

PIKE'S CORNERS

FDA Approves New Treatment for Rare Leukemia

HHS Trumpets 'Medical Breakthrough' at Press Conference

WASHINGTON—FDA on May 10 announced the approval of imatinib mesylate (Gleevec, also known as STI-571), a promising new oral treatment for patients with chronic myeloid leukemia—a rare life-threatening form of cancer. FDA reviewed the marketing application for imatinib in less than three months under its accelerated approval regulations.

The drug was hailed as a "medical breakthrough" by HHS Secretary **Tommy G. Thompson** at a press conference, an unusual event for FDA drug approvals. The action marks the approval of the first drug that directly turns off the signal of a protein known to cause a cancer. Other previously approved molecular-targeting drugs interfere with proteins associated with other cancers, but not with proteins that directly cause the disease (page 9).

"FDA and Novartis, the drug's manufacturer, should be commended for the rapid development and review that will make this product available soon for the leukemia patients who desperately need it," said Thompson. "It is also important to recognize that today's approval is also a culmination of years of work and years of investment, by many people in many different institutions, and even in different fields of medicine. It's a testament to the groundbreaking scientific research taking place in labs throughout America."

FDA approved the drug for treating patients with three stages of CML: CML myeloid blast crisis, CML accelerated phase, or CML in chronic phase after failure of interferon treatment. Accelerated approval allows FDA to approve drugs for serious or life-threatening ill-

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Report to Nation Shows Balance in CDER Programs

The fifth edition of the Center's performance report, *CDER 2000 Report to the Nation: Improving Public Health Through Human Drugs,* is available on CDER's Web site. Direct links to the report can be found on the About CDER page or on page 10 of this issue.

Center Director **Janet Woodcock, M.D.,** noted in an introductory message that CDER continued its efforts last year to strike the right balance in its programs.

"We have worked hard to provide rapid access to new therapies while maintaining rigorous safety and effectiveness standards," she said, "to listen to the voices of consumers, patients and health care professionals as well as those of regulated industry; to match the effort in premarket evaluation with a vigorous postmarket monitoring program; and, of course, to make sure we support the people in CDER as well as serving the outside world."

The report's four chapters contain statistics, graphs, charts and descriptions of the Center's

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Internal Reference Guide to Replace *Quick Index*

The *CDER Internal Reference Guide,* which is designed to help you locate subject matter experts and their phone numbers, is available on CDER's intranet at http://cdernet/dcm/irg.htm.

The guide is for internal use only and replaces the *CDER Quick Index '98.* Questions from outside the Center should be directed to the Division of Drug Information at 1-888-INFO-FDA.

The guide's editor, **Christine Parker,** a public information specialist in OTCOM's Division of Public Affairs, has been working on the project since November.

"I was really pleased with the excellent cooperation I received from the CDER administrative staff," Parker said. "I had a 100 percent response rate, and more than 75 percent of the information has changed."

(Continued on page 10)

JOE'S NOTEBOOK

Spring Fling

Like many universities, mine held a primitive bacchanalian rite called "spring fling" that marked the passing of winter. In my senior year, spring fling was memorable for its snowstorm. Most of us went home, but a few hearty souls continued their revels despite being snowed under.

Similarly, the April issue of the *News Along the Pike* was snowed under by production of the *CDER 2000 Report to the Nation* (page 1). Our annual performance report is a treasure trove of statistics and basic information. You can cut-and-paste the charts right into your presentations. See page 10 for the Internet address of the presentation slides.

We are ordering some commercially printed copies and will send several hundred to Center components. If you'll need some for an upcoming presentation or meeting, let me (OLIVERN, 7-1695) know soon, before we hand them all out. If you're outside CDER and need individual printed copies, please call the Drug Information Division at 1-888-INFO-FDA.

The report wouldn't be possible without a great deal of help and cooperation from throughout the Center.

- *Office of the Center Director.* Input from **Randy Levin, Justina Molzon, Jim Morrison** and **Janet Woodcock.** Proofreading from **Nancy Derr** and **Susan O'Malley** from the Regulatory Policy Staff.
- *Office of Review Management.* **Elaine Abraham, Nancy Maizel** and **Ann Myers** from the Reports and Data Management Team that coordinates the statistical and analytical drug review data for ORM. **Terrie Crescenzi** for data on pediatric exclusivity and **Dianne Kennedy** for information on pregnancy labeling. **Linda Katz** for information from the Division of Over the Counter Drug Products.
- *Office of Medical Policy.* **Bob Temple** for a careful reading. **Carolyn Hommel** and **Stan Woollen** for data on activities from the Division of Scientific Investigations. **Melissa Moncavage** and **Nancy Ostrove** for data from the Division of Drug Marketing, Advertising and Communications.
- *Office of Pharmaceutical Science.* **Jonathan Cook, Kathy Jordan, Ted Sherwood, Marilyn Welschenbach,** who coordinated the OPS effort, and **Helen Winkle. Gary Buehler, Greg Davis, Rita Hassall** and **Ruth Warzala** for information from the Office of Generic Drugs. **Wes Metz** from the Office of Clinical Pharmacology and Biopharmaceutics. **Ajaz Hussain** and **David Morley** from the Office of Testing and Research.
- *Office of Compliance.* **Brian Hasselbalch, Erik Henrikson, Brenda Holmes,** who coordinated OC's input, **Roxana Newquist, Lana Ragazinsky,** and **Michael Verdi.**
- *Office of Post-Marketing Drug Risk Assessment.* **Roger Goetsch** and **Peter Honig.**
- *Office of Training and Communications.* **Carol Assouad, Pat Clarke, Sherunda Lister, Norman Marks, Janice Newcomb, Barry Poole, Ellen Shapiro, Tony Sims** and **Wendy Stanfield,** who designed the cover for the printed edition.
- *Office of Information Technology.* **Robert Reinwald** for the manufacturer's mailing list.

Finally, many of the descriptions of newly approved drugs are lifted from FDA's January 18 Talk Paper on approvals in 2000 written by **Mike Kubic** from the Agency's Press Office.

Spring Fling II: Norman Marks, MedWatch's medical director, would like to link up with any *Pike* readers among the 1,700 bikers taking part June 21 to 24 in the 330-mile AIDS Ride from Raleigh, N.C., to Washington.

news along the pike

The Pike is published electronically on the X:drive in Cdernews and on the World Wide Web at:

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

Photocopies are available in the Medical Library (Parklawn Room 11B-40) and its branches (Corporate Boulevard Room S-121 and Woodmont II Room 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 comments to contribute?
Please contact a member of the Editorial Board or:

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OMBUDSMAN'S CORNER

To Err Is Human, To Admit It Sublime

BY JIM MORRISON

People who do not admit they made a mistake, particularly when the mistake is obvious to all around them, are sometimes likened to an ostrich burying its head in the sand.

Although ostriches lack some social graces, that characterization does them a disservice. When an ostrich appears to bury its head in the sand, it is actually putting its ear to the ground to better hear the approach of predators. That leaves humans who refuse to admit mistakes pretty much in a class by themselves.

It's bad enough when individuals do it, but when organizations refuse to admit mistakes, it infuriates those who are affected by the error. Remember the tobacco company executives with their right hands in the air, swearing before Congress that cigarettes don't cause health problems? Unfortunately, it is an exceptional organization that does not commit the *faux pas.*

So what should those of us who work in CDER do if we realize we have made a mistake? First, we shouldn't panic. Everyone makes mistakes. It's what distinguishes humans from inanimate objects. Next, assuming it is a mistake that has some significance, we should tell someone about it, preferably our supervisor. In that way, we save our supervisor from getting blind-sided about the error later.

Whatever we do, we should not deny the mistake was made. And we must never, never try to cover it up. Occasional errors may or may not get noticed. However, covering up errors often gains headlines. Richard Nixon was not impeached for the Watergate break-in; he was impeached for trying to cover it up.

> "Yet, rarely do I hear anyone admit in a meeting with the distressed party that any mistakes were made."

That brings me to the reason for my column this month. Many of the cases that come to my desk have a history of one or more errors that could have been avoided by CDER staff. Once in a while, those errors form the basis of an appeal, or, at least, lend credibility to a company's complaint.

Yet, rarely do I hear anyone admit in a meeting with the distressed party that any mistakes were made. Sometimes they are glossed over, and other times they are explained in a manner that absolves an individual but still leaves the Agency in a bad light.

Invariably, the company representatives are incensed, making an amicable resolution of the issues more difficult. You won't see company representatives turn red and pound the table, given the realities of the regulator-regulated relationship. However, they become more entrenched in their positions and less amenable to meeting the Agency half way. I wonder, if those meetings had opened with an admission that mistakes were made and regretted, how much time, resources and ill will could have been saved.

We say that individually we want reputations for honesty, credibility and trustworthiness. The CDER operating principles also seek to establish such a reputation for our organization. Admitting our mistakes, both individually and organizationally, is the key to attaining that reputation.

Jim Morrison is the Center's ombudsman.

EEO CORNER

Center Makes Annual Commitment to Hiring 26 Persons with Disabilities

BY MARGARET BELL

To comply with FDA's plan for ensuring that persons with disabilities have increased opportunities for federal employment, CDER will be expected to hire a minimum of 26 disabled employees per year for the next five years.

Currently, we employ 89 permanent employees with reported disabilities, representing 5.7 percent of the Center's workforce.

To accomplish our goal, we are expected to expand our external and internal recruitment and increase efforts to accommodate individuals with disabilities. All activities involving the employment of persons with disabilities will count, including Schedule A and special hiring authority appointments, temporary hires, summer (High School-High Tech) and other internship programs.

As you review your hiring plans for the remainder of the year, please remember our commitment to provide employment opportunities for people with disabilities. Your personnel specialist and the EEO staff are available to assist you in the recruitment, retention, advancement and provision of reasonable accommodations to both present and future employees.

Copies of *Food and Drug Administration Plan for Employment of People with Disabilities in the Federal Government* will be distributed to all managers and supervisors.

The plan was developed as a result of directives issued last year from the Office of Personnel Management and the Department of Health and Human Services.

The plan provides the framework and guidance for addressing two executive orders issued last July.

These orders set forth requirements for federal agencies on increasing the opportunities for individuals with disabilities to be employed in the federal government and requiring federal agencies to establish procedures to facilitate the provision of reasonable accommodation. An additional executive order mandated all federal agencies hire 100,000 persons with disabilities over the next five years.

FDA and other HHS agencies were required to provide hiring estimates to the department. Based on a formula developed by the department, FDA is committed to hiring 106 individuals with disabilities annually for the next five years.

Margaret Bell heads the Center's EEO Staff.

INFORMATION TECHNOLOGY CORNER

Sign Up for Just-in-Time Electronic Submissions Training

The Technology Support Services Staff is now making its NDA Electronic Submissions Training, NDA Electronic Data Analysis Training and JMP training available for reviewers as they receive an electronic new drug application. With this method, the training is fresh when the submission is received.

Project Managers are asked to assess needs for computer training at pre-NDA meetings and then contact **Lana Kostecka** (KOSTECKAL) or **Tim Mahoney** (MAHONEYT) to arrange just-in-time computer training for members of that NDA team.

These training classes are in addition to the regularly scheduled desktop and electronic submission classes that OIT holds monthly.

All CDER staff are encouraged to attend classes as needed. Consult the Training section of the OIT intranet site (http://oitweb) for training dates, course descriptions and registration.

Security Reminders

Information security is very important. Because information is what we deal in and much of our information is not public information, it must be protected. Here are some important security reminders:

- Turn off your PC at the end of the day. Rebooting will update the anti-virus software we use if an update has been issued. The software is normally updated once a week but may be done more frequently if necessary due to new viruses being introduced. We don't announce the viruses but do take steps to prevent them to the extent possible.
- Never give your password to anyone, including OIT staff, Help Desk staff or investigators. Passwords must be at least seven characters long and should contain numbers as well as letters. Never use any easily guessed password such as your address, your spouse's name or your pet's name. Passwords must be changed at least every three months.
- No software should be loaded on your PC, including software downloaded from the Internet, without OIT approval.
- Personal, non-work use of the Internet must be on your own time, either before work, during lunch, during a break, after work or on weekends.
- Any suspected security violations should be reported to your supervisor or the CDER information systems security officer, **Dave Moss** (MOSS).
- If you haven't completed the on-line FDA Computer Security Training, please do so as soon as possible. It's required training. It takes about 20 minutes to complete and can be found at http://intranet.fda.gov/oirm/itsecurity/training.
- Please be extra careful in using laptops. When you go on a trip, they can't be packed in your luggage; they're too fragile. Laptops are a frequent target for thieves. In fact, there is an epidemic of laptop thefts in airports in this country and it's even worse overseas. Don't leave laptops unattended in your car. Never give a laptop to someone who says he or she is a repair person. Only give it to your property officer or a known Help Desk technician if repairs are needed.

Help Desk FAQ

Yes, it happens. Yes, it's stressful. Yes, it's recoverable.

We are talking about hard drive failures. Don't lose important data. Backup the data on your hard drive at least once a week and protect yourself and valuable CDER data.

Data can be copied to:

- Floppy disks.
- Jaz or Zip drives purchased by your division.
- Burned to a CD on a CD reader-writer purchased by your division.

OIT technicians are on hand to assist you with the installation of external drives such as Jaz drives or CD writers and to show you how to use them.

Contact the Help Desk (HELP, CDER HELPDESK in Outlook) for more information.

June IT Training

- **Monday, June 4:** Outlook Refresher (C) 9:00-11:00; Outlook Refresher (C) 1:00-3:00.
- **Friday, June 8:** Outlook Refresher (C) 9:00-11:00; Time Reporting (P) 9:00-12:00; Outlook Refresher (C) 1:00-3:00; Time Reporting (P) 1:00-4:00.
- **Monday, June 11:** Time Reporting (P) 9:00-12:00; Excel (C) 1:00-4:00; Time Reporting (P) 1:00-4:00.
- **Tuesday, June 12:** Word Intro (C) 9:00-12:00; Time Reporting (P) 9:00-12:00; Word Formatting (C) 1:00-4:00; Time Reporting (P) 1:00-4:00.
- **Wednesday, June 13:** Word Tables (C) 9:00-12:00; Outlook Refresher (P) 9:00-11:00; Creating PDFs (C) 1:00-4:00; Outlook Refresher (P) 1:00-3:00.
- **Thursday, June 14:** E-doc (C) 9:00-12:00; DFS (C) 1:00-4:00.
- **Monday, June 18:** Outlook Refresher (C) 9:00-11:00; Outlook Refresher (C) 1:00-3:00.
- **Wednesday, June 20:** NEST (C) 9:00-12:00; NEDAT (C) 1:00-4:00.
- **Tuesday, June 26:** DFS (C) 9:00-12:00; AERS Datamart (C) 1:00-4:00.
- **Wednesday, June 27:** PEDS (C) 9:00-12:00.

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

Go to http://oitweb and click on the Training button to access training registration and resources.

Center Launches Drug-Induced Liver Toxicity Web Site

A new CDER Web site contains the study documents, program and abstracts of presentations at the conference "Drug-Induced Liver Disease: A National and Global Problem" held in February and co-sponsored by CDER, PhRMA and the American Association for the Study of Liver Diseases (January *Pike*).

Among patients with acute liver failure evaluated at U.S. liver transplantation centers, ingestion of drugs has become the leading cause for liver failure, exceeding all other causes combined. The Web site is part of continuing cooperative efforts to identify and define issues, to develop and agree upon research agendas and to educate physicians and patients.

PEDIATRICS CORNER

Abrams Lecturer Discusses History, Ethics, Adverse Events

BY PATRICK E. CLARKE

The 2001 William B. Abrams Lecture, "Drug Development and Therapeutics: What Our Children Have Taught Us," was delivered March 14 by Stephen P. Spielberg, M.D., Ph.D., vice president of pediatric drug development at the Janssen Research Foundation in Titusville, N.J.

More than 200 people heard Dr. Spielberg discuss the history of pediatric drug development, the ethics of clinical trials using children and the major causes of adverse events when using medicines in children.

Historically, pediatric drug development was minimal because of the absence of regulations, the vulnerability of the pediatric population and the rarity of some diseases such as inborn errors of metabolism. However, in 1995, the American Academy of Pediatrics Committee on Drugs concluded that nonvalidated use of medicines places children at greater risk than participation in well-controlled, ethically conducted clinical trials.

Dr. Spielberg also explained that science has improved to match the needs of pediatric studies. For example, a blood draw from premature infants used to require 10 milliliters, which could be a fourth of their blood supply. Due to improved instrumentation and new technology, a much smaller amount is needed.

He gave some of the greatest credit for pediatric drug development's rapid progress over the last several years to the pediatric exclusivity provisions of 1997 FDA Modernization Act and the 1998 pediatric rule that requires pediatric studies for newly approved drugs. These legislative and regulatory changes have led to the establishment of a pediatric infrastructure within drug companies. The expansion of pediatric investigative activity has led to development of career paths in industry, academia and government.

Dr. Spielberg stressed the need to obtain feedback from children not only on how a drug worked in a clinical trial but also on how the trial was conducted. "Children must never be commodities," he said, "they must be our human partners, and we must respect their individual autonomy."

Growth and development factors must be taken into account when designing pediatric studies, Dr. Spielberg said. For example, if a drug cures the disease, but damages the child's growth plates, this fact should be discovered and evaluated during a clinical trial.

There have been substantial benefits related to pediatric clinical trials. Dr. Spielberg indicated that 95 percent of children with cancer in this country participate in Children's Oncology Group protocols. Subsequently, there has been a 40 percent decrease in cancer mortality in children during the last 20 years as opposed to six percent in adults.

He said the primary causes or origins of adverse effects in children are formulation-related, dose-related, idiosyncratic, developmental and those due to some unique features of the newborn.

The pharmacokinetics of a drug must be well-studied because children from toddlers up to puberty clear many drugs more rapidly than adults and may be at risk for underdosing. On the other hand, premature babies have limited clearances by both metabolic and renal pathways and are at risk for drug accumulation.

Dr. Spielberg concluded by stating that there are no easy answers to pediatric drug development. There will continue to be a need for targeted and directed pharmacokinetic pediatric drug studies. He said the best approach to the complex issues ahead is to form partnerships between clinicians, legislators, regulators, industry, parents and patients. "We will never know everything," Dr. Spielberg said. "Yet, being successful in medicine and helping sick children requires action in the absence of full knowledge."

The lecture series, named for William Abrams, M.D., who died in 1999, is cosponsored by the American Society for Clinical Pharmacology and Therapeutics (February, *Pike).* Videos of the lecture are available in the Medical Library and its branches. Copies of the slides are at http://cdernet.cder.fda.gov/dtd/SEMINARS/Spring01/abrams.ppt.

Patrick Clarke is a public affairs specialist in OTCOM

Interim Rule Establishes Additional Safeguards for Pediatric Clinical Trials

FDA on April 24 issued an interim rule to provide additional safeguards for children enrolled in clinical trials of medical products the agency regulates. This action was mandated by the Children's Health Act of 2000 that calls for specific measures to better promote the unique needs of children participating in clinical trials.

The new rule is designed to help the Agency and clinical researchers address many of the ethical issues that will accompany the expected increase in the enrollment of children in clinical trials.

Recent initiatives such as the agency's 1998 pediatric rule and the pediatric exclusivity provisions of the 1997 FDA Modernization Act have encouraged sponsorship of more pediatric clinical trials that can provide vital information about how therapeutic drugs and devices work specifically in children.

These data can provide important insight into how these products can be formulated, administered and labeled in ways that maximize their benefit and minimize their risk to children.

Under the new regulation, institutional review boards responsible for maintaining safeguards for clinical trial subjects will now have specific standards for determining whether proposed pediatric clinical trials can be ethically conducted.

A key aspect of the new rule sets standards and procedures for assuring that children have assented to participating in clinical trials (when possible), and that their parents or guardians are able to give fully informed consent to the child's participation in a study.

Written comments on the rule can be submitted to FDA for 90 days following its publication. The interim rule can be found at http://www.fda.gov/ohrms/dockets/98fr/042401a.pdf.

TRAINING AND DEVELOPMENT CORNER

Center Offers Myers Briggs Type Indicator Workshop

The Division of Training and Development offers a workshop in the Myers Briggs Type Indicator. Participating in the workshop can help you better understand yourself and your interactions with your colleagues, friends and family.

The psychological test used in the workshop was developed by Isabel Briggs Myers and Katherine Briggs in the early decades of the 20th century. They designed it as a tool to capture information related to the theories of Swiss-born psychiatrist Carl Jung. Jung believed that everything we do is tied either to gathering information or making decisions based on the information we gather. According to Jung, human behavioral differences result from preferences that form the foundation of our personalities.

Using Jung's theories, Myers and Briggs designed a written questionnaire to determine people's preferences. This questionnaire is one of the most widely used psychological instruments.

According to Myers and Briggs, your personality preferences are:

- Extraversion or introversion.
- Sensing or intuition.
- Thinking or feeling.
- Judging or perceiving.

Jung believed that people find their source of energy either internally or externally. This preference is represented by the extraversion-introversion dichotomy.

The sensing-intuitive dichotomy represents the way we gather information. The manner in which we make decisions is represented by the thinking-feeling dichotomy.

Myers and Briggs' fourth dichotomy assesses your functional preference. In essence, do you prefer to gather information or make decisions? This preference is represented by the judging-perceiving dichotomy.

Your Myers Briggs Type is a combination of each of the four dichotomies.

Think of the instrument as a mirror that gives you an opportunity to see yourself from a different perspective. The test neither measures the quality of your preference nor predicts your ability to perform a particular task. It allows you to self-report your preferences and self-validate how those preferences influence your personal style of actions and interactions with others. It will also help you recognize the different styles of human interaction.

DTD has two certified administrators who can offer either half-day or full-day workshops for work groups such as offices, teams and committees. Workshop participants frequently find common ground by recognizing different personality styles within their work group.

If you would like to learn more or schedule a workshop for your office, please contact **Janice Newcomb** (NEWCOMBJ, 7-4580) or **Dorrie Ballmann** (BALLMANND, 7-3490).

RSR Explained

BY MARY FANNING AND CAROL NORWOOD

RSR is an unusual acronym and doesn't stand for the whole title of the program—Regulatory Science and Review Enhancement. The RSR Subcommittee, a component of the Research Coordinating Committee, manages the program.

Regulatory science and review enhancement broadly refers to any activity involving the exploration of approaches, methods or data that could enhance the quality or efficiency of the review process for new and investigational drugs. It also includes the design and evaluation of clinical and nonclinical protocols.

The subcommittee solicits proposals for funding of projects from Center scientists. The new knowledge and the development of new methods in regulatory science resulting from these projects should facilitate:

- Making better use of information already available to the Center.
- Reaching our regulatory objectives more effectively.
- Disseminating relevant scientific information to industry for planning and designing future drug trials and drug development.

Another purpose of these projects is to support the professional growth of our scientists through professional development activities.

Within the next few months, the subcommittee will announce both funding for fiscal 2002 and some of CDER's priorities for this type of research. We hope that there will be projects from all the major components and disciplines within CDER. The RSR site on the CDERnet at http://cdernet.cder.fda.gov/ocd/rsr.htm lists the currently funded projects and provides more detailed information about RSR. Keep watching for RSR information in e-mails, in *News Along the Pike* and on CDERnet.

Mary Fanning is Associate Director for Medical Affairs in OGD and serves as chairperson of the RSR Subcommittee. Carol Norwood is in Executive Operations Staff and serves as project manager on the subcommittee.

PIKE'S PUZZLER

AKA Quiz

BY TONY CHITE

Some medical names are also known as (AKA) another term. Match the number on the left to the letter on the right.

1. riboflavin	a. amytrophic lateral sclerosis
2. quicksilver	b. rales
3. farsightedness	c. vitamin B-1
4. Lou Gehrig's disease	d. myopia
5. shin bone	e. stapes
6. crackle	f. presbyopia
7. fainting	g. syncope
8. stirrup	h. tibia
9. thiamine	i. vitamin B-2
10. nearsightedness	j. mercury

Key: 1i, 2j, 3f, 4a, 5h, 6b, 7g, 8e, 9c, 10d

Tony Chite is a CSO and pharmacist in the Division of Freedom of Information.

FDA Requests Increased Funds to Strengthen Health Protections

The president's budget request for FDA in fiscal year 2002, which begins Oct. 1, totals $1.414 billion, an increase of $123 million or 9.5 percent more than in fiscal year 2001. The budget request, which includes $204 million in industry-specific user fees and was announced April 9, reflects FDA's commitment to continue strengthening the public health protection by focusing on urgent public health hazards and major performance goals emphasized by Congress.

Here is a breakdown of the requested appropriations increase:

- $10 million to safeguard patients against adverse events associated with the use of drugs, biological agents and medical devices by improving FDA's system for monitoring marketed products. Plans for using the requested funds include strengthening the Agency's capacity to learn about, identify and respond to adverse events; increase education programs for dietary supplements; and educate consumers and health-care professionals about the importance of preventing and reporting medical errors.
- $10 million to protect the human subjects and the integrity of research data in clinical trials by increasing FDA's inspections. FDA currently performs about 1,100 trial-associated inspections a year, less than 4 percent of the 30,000 clinical sites testing FDA-regulated products. The request will be used to increase the number of inspections by one-third; focus them on high-risk studies; and cover clinical investigators, institutional review boards, sponsors, monitors and contract research organizations.
- $15 million to protect consumers against new variant Creutzfeldt-Jakob disease, a fatal illness associated with consumption of meat from cows with bovine spongiform encephalopathy. The request is designed to ensure the strengthening of and 100 percent compliance with FDA guidances and rules to help prevent the spread of BSE and nvCJD through FDA-regulated products, including drugs, biologics, medical devices, pet foods, food additives and dietary supplements.
- $17.3 million to enhance FDA's scientific potential and operational efficiency through infrastructure improvements. This includes $6 million to equip and occupy a new CDER laboratory as part of the consolidation at White Oak; $8.3 million for the development of an advanced financial management system; and $3 million for the completion of a new laboratory in Los Angeles.
- $40 million to meet mandated cost-of-living and pay-related increases for FDA's employees. In the last eight years, FDA has had to absorb $284 million in unfunded pay raises and other inflationary costs by reducing its staffing of all programs not supported by user fees from 8,996 to 7,908. During the same period, research and development spending by the pharmaceutical industry and the National Institutes of Health increased from approximately $22 billion to almost $45 billion. The request will enable the Agency to maintain current levels of performance, and support about one-half of the staff that reviews generic and other drugs not covered by user fees.
- $25 million ($10.3 million in budget authority and $14.7 million in new import user fees) to prevent substandard food and health care products from reaching the U.S. market by increasing plant inspections and expanding surveillance of regulated imports.
- $14.7 million ($9.4 million in budget authority and $5.3 million in new user fees) to significantly upgrade food safety by expanding the highly successful Food Safety Initiative beyond microbiological contaminants to cover chemical and physical food hazards.

FDA is also requesting new user fees—$15 million for import activities and $5 million to provide certifications for food exporters—and several increases in current user fees, including $12 million (of the total $162 million) requested for drug and biologic reviews under the Prescription Drug User Fee Act of 1992.

For more details, see the FDA backgrounder at http://www.fda.gov/opacom/backgrounders/budget.html.

Drugs in the News: 2nd HFA Inhaler OK'd; Warnings on Opiate Abuse Drug

FDA on April 20 approved albuterol sulfate HFA (Ventolin HFA), a new version of the Ventolin metered-dose inhaler for asthma and other obstructive lung diseases. The approval means that there are now two albuterol HFA metered dose inhalers approved in the United States. HFA inhalers use hydrofluoroalkane to propel the medication rather than chlorofluorocarbons. Since 1978, the use of CFC-aerosol products in the United States has been sharply curtailed because of increasing evidence that CFCs contribute to the depletion of the Earth's protective ozone layer

On April 20, FDA announced it has changed labeling for the opiate addiction treatment levomethadyl (Orlaam) to increase the strength of the warnings about serious cardiac adverse events associated with and to highlight these warnings in a black box. In addition, the approved indication for levomethadyl will be revised to indicate that the drug is not to be used as first line therapy. As of March 30, 10 cases of serious arrhythmias have been submitted to FDA through MedWatch. An estimated 33,000 patients have been treated with levomethadyl to date.

FDA issued a public health advisory May 9 to announce important safety-related updates to the labeling of itraconazole (Sporanox) and terbinafine hydrochloride (Lamisil Tablets). FDA is advising healthcare professionals not to prescribe itraconazole to treat fungal infections (onychomycosis) in patients who have congestive heart failure or a history of CHF. The updated terbinafine labeling also includes contraindications and precautions with certain medicines. More information is on the CDER Internet site at http://www.fda.gov/cder/drug/advisory/sporanox-lamisil/default.htm.

Kobayashi: 'Rising Star' Training Focuses on Public Service

BY MARY-JANE ATWATER

Imagine what it would be like to study and debate government philosophy—entirely in Japanese—for two weeks with 39 Japanese government officials from different and unrelated professional fields. CDER's **Ken Kobayashi, M.D.,** a medical officer in the Division of Oncology Drug Products, recently discovered firsthand the unique challenges and the value of this experience. He attended a two-week training program that the government of Japan offers its rising stars in middle management.

In January, Dr. Kobayashi, who is spending a year in Japan as a Mike Mansfield Fellow, took a two-week leave from his placement at Japan's Ministry of Health and Welfare in order to become one of three U.S. trainees in a Japanese government-sponsored administrative training program.

"I've never attended anything quite like this course," Dr. Kobayashi said. "At FDA, we have retreats with our work team or attend conferences with others in our field. But in Japan, the participants at each training course are drawn from a large number of Japanese ministries and agencies, local and regional governments, private companies and universities. The training I attended brought together people from diverse backgrounds and required us to work together and listen to each other in a way that often challenged long-held opinions and assumptions."

Japan's administrative training course is typically split into two one-week sessions. The first week of the course was held at a Tokyo training center. Each day, participants attended a series of didactic lectures on Japanese politics and economics, and they were assigned to a *han,* or small group, in preparation for the activities of the second week. During the second week, participants relocated to a residential training center in Iruma City about 45 minutes from Tokyo.

The focus of the second week was a series of small group activities, including individual presentations by participants and a formal debate among the *han,* the basic unit of the of training course.

Kobayashi admits that listening to lectures lasting two to three hours each during the first week was less than exciting. The lectures were entirely in Japanese and focused on such topics as budget development in government agencies and economic issues in Japan. The speakers did not use visual aids or permit short breaks.

Kobayashi observed that the real value of the course resides in the work of the *han.* On the first day of the course, the class was split into six *han,* and each group was assigned one of the three debate topics:

- The role of central vs. local government authority.
- Administrative neutrality.
- The separation of political and bureaucratic powers.

Trainees became integrated in the *han* not only by collaborating on debate preparation but also through after-hours socializing with the group.

During the second week of the training course, Dr. Kobayashi's *han* met daily to prepare for its debate on the role of central vs. local authority. In addition, each participant made a 30- to 45-minute individual presentation to the *han* on a topic of his or her choice.

Dr. Kobayashi gave an overview of FDA and described how CDER functions. Emphasizing FDA's team approach, he spoke about the drug review process for both investigational and new drugs. Other participants spoke on such topics as Japan's new personnel evaluation system, problems with implementing freedom of information in Hokkaido and countermeasures to prevent medical errors. Each presentation was a springboard for a follow-up discussion that allowed for a candid exchange of differing viewpoints.

The second week concluded with debates among *han,* with two small groups assigned to each of the three debate topics. Each hour-long debate consisted of a presentation by the two *han,* questions from the opposing side and audience questions. The instructor concluded with a summary, but no winner was determined. Dr. Kobayashi observed that although everyone in his class used a PowerPoint presentation, familiarity with the software was surprisingly limited, and he was able to step in and improve the format of his group's presentation.

"The primary goal of this training course is to build relationships with a network of people who will be the next leaders in Japan's government," Dr. Kobayashi said. "Even though there was often a language barrier between other participants and me, the course accomplished this goal. We all had an unparalleled opportunity to step outside the narrow stovepipe of the Japanese bureaucracy and gain a broad understanding of our role as public servants. If such a program were available in the United States, it would be a valuable opportunity for federal employees to take off the blinders, hear new perspectives, and work together more effectively."

Dr. Kobayashi's fellowship will conclude in September, and he will return to the Center.

CDER is well-represented in the Mansfield Fellowship Program. When he returns from Japan, Kobayashi will join a second Mansfield Fellow alumnus, **Hank Malinowski, Ph.D.,** acting director of the Division of Pharmaceutical Evaluation II, who was a Mansfield Fellow 1998-2000. **Monica Caphart,** compliance officer in the Office of Compliance, was named a Mansfield Fellow last year and has been in training since September. She will begin her placements in Japan in September 2001. A fourth FDA employee, **Ronda Balham**, from the Office of Orphan Drug Products Development, is also a Mansfield Fellow scheduled to go to Japan in September.

Established by Congress in 1994, the Mansfield Fellowships are building a core group of U.S. government officials who serve as a resource to their agencies on issues involving Japan. The fellowships provide for a year in Japan working full-time in professional positions in Japanese government offices, preceded by a first year of intensive, full-time study in the United States of the Japanese language and area studies.

More information about the program is available at http://www.mcpa.org.

Mary-Jane Atwater is director of communications at MCPA.

NCI PERSPECTIVE

Imatinib Hailed as New Way to Think about Cancer Treatment

BETHESDA—The National Cancer Institute says that imatinib mesylate (Gleevec) represents a new class of cancer drugs and a new way of thinking about treating cancer. These molecularly targeted drugs are different because they target abnormal proteins that are fundamental to the cancer itself.

Most current cancer therapies lack specificity, killing both cancer and normal cells. This is one reason why many people who undergo chemotherapy experience unwanted side effects from their medications.

However, imatinib and other drugs in development are designed to zero in on specific cancer-causing molecules, eliminating cancer cells while avoiding serious damage to other, non-cancerous cells.

In the case of imatinib, the drug is targeted at the Bcr-Abl protein in chronic myeloid leukemia cells. Imatinib also affects other messenger systems in a cell, which may contribute to its toxicity.

NCI scientists note that a number of important questions about imatinib remain to be answered. These include:

- How long does imatinib control CML?
- Does imatinib actually cure patients of CML? Or, does the drug delay the onset of more advanced forms of the cancer? If so, how long does imatinib keep CML in check?
- Can the effectiveness of imatinib be enhanced in combination with other drugs?

> "Gleevec offers proof that molecular targeting works in treating cancer, provided that the target is correctly chosen. The challenge now is we've got to find these targets."
>
> *—Richard Klausner, M.D.*
> *NCI Director*

Imatinib does not help all people with CML. Because imatinib is a molecularly targeted drug, it will only be effective in cancers in which a target protein is present and involved in causing the tumor.

In addition to Bcr-Abl, imatinib may also target the cellular proteins c-kit and platelet-derived growth factor receptor.

Several clinical trials with imatinib are already under way to find other tumors that might respond to imatinib. Currently, these tumors are gastrointestinal stromal tumor, glioma and soft tissue sarcoma.

41-Year-Old Discovery Set Stage for Molecularly Targeted Therapy

NCI notes that imatinib builds on an observation that was first made in 1960.

"Like most scientific breakthroughs, this one is not sudden, nor does it stand alone," said HHS **Secretary Tommy G. Thompson.** "Rather, like most scientific advancement, it is a culmination of years of work and years of investment, by many people in many different institutions, and even in different fields of medicine."

Key dates on the road to imatinib are:

1960: Peter Nowell reports that patients with chronic myeloid leukemia consistently had an abnormally small chromosome 22, an alteration that became known as the Philadelphia chromosome, named after the city where the research was conducted. Because of the consistency of the finding, scientists speculate that this shortening might be related to the cause of the leukemia.

1973: New staining techniques allow researchers to see that, in addition to the deletion in the long arm of chromosome 22, the long arm of chromosome 9 is lengthened by about the same amount in all the CML patients examined. This suggests that pieces of each chromosome are exchanged or translocated.

1982: One of the human cancer genes, the Abl proto-oncogene, is shown to be located on chromosome 9 in non-CML patients and translocated to the Philadelphia chromosome in patients with CML. These findings raise the prospect that the Abl oncogene is activated by this translocation.

1984-1987: During this period, several labs play a role in discovering how the translocation produces a cancer-causing protein. They find that in cancer cells, the Abl translocation to chromosome 22 leads to the formation of an altered protein containing a piece of the Abl protein joined to a piece of a second protein, Bcr. It is this fused protein product, called Bcr-Abl, which is abnormally expressed in about 95 percent of CML patients.

1990: Several labs show that Bcr-Abl alone causes leukemia in mice.

1993: The first laboratory studies of STI-571 (as imatinib is known at the time) begin when scientists now at Oregon Health Sciences Center in Portland and Novartis Pharmaceuticals in Basel, Switzerland, designed the chemical structure of STI-571 so that it would block the abnormal protein, Bcr-Abl.

1996-1997: STI-571 is shown to inhibit the growth of Bcr-Abl-expressing laboratory cells.

1998: STI-571 is first tested in a small study in people to determine whether it is safe. Doctors notice that with higher doses, patients had dramatic positive responses to the drug.

1999: The preliminary results of this early study show that 31 out of 31 patients who received at least 300 milligrams daily had their blood counts return to normal. In nine of the 20 patients who were treated for five months or longer, no cells with the Philadelphia chromosome could be found.

February 2001: Novartis submits its new drug application for STI-571, now named Gleevec, for the treatment of the late phases of CML.

April 2001: Results of a larger study of STI-571 in 83 patients are reported in *New England Journal of Medicine.* In the 54 chronic-phase CML patients who were treated with doses of 300 milligrams or more, normal blood counts were restored in 53, and in 29 of the 54 patients, the Philadelphia chromosome disappeared. Most side effects were mild.

May 2001: CDER approves the sale of imatinib for CML.

HHS Trumpets Approval of Molecularly Targeted Treatment for Leukemia

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nesses on the basis of clinical trials establishing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict a real clinical benefit. Imatinib has been shown to reduce substantially the level of cancerous cells in the bone marrow and blood of treated patients.

FDA approved imatinib under FDA's orphan drug program, which provides financial incentives for drugs developed to treat rare diseases.

"Although the long-term benefits of the drug are not yet known, early studies have shown that imatinib will offer a significant improvement for many patients," said FDA Acting Commissioner **Bernard A. Schwetz, DVM, Ph.D.**

"However," he said, "further studies are needed to evaluate whether imatinib provides an actual clinical benefit, such as improved survival, as well as to examine its effect when used in early stage disease."

Dr. Schwetz also said that it is important for physicians and patients to understand currently known side effects from imatinib, and to realize that additional side effects may be discovered with more follow-up of patients in ongoing studies.

Chronic myeloid leukemia occurs when pieces of two different chromosomes break off and reattach on the opposite chromosome, forming the so-called "Philadelphia" chromosome.

This chromosome translocation leads to a blood cell enzyme being "turned on" all the time. As a result, potentially life-threatening levels of both mature and immature white blood cells occur in the bone marrow and the blood.

Imatinib, an inhibitor of the translocation-created enzyme, works by blocking the rapid growth of white blood cells.

"For the first time, cancer researchers now have the necessary tools to probe the molecular anatomy of tumor cells in search of cancer-causing proteins," said **Richard Klausner, M.D.,** director of the National Cancer Institute. "Imatinib offers proof that molecular targeting works in treating cancer, provided that the target is correctly chosen. The challenge now is we've got to find these targets."

> Review time: "an all-time record for the evaluation of a highly complex, novel drug."
> —*Tommy G. Thompson*

Symptoms of leukemia may include abdominal discomfort, bone and joint pains and fatigue. Some patients are diagnosed when a routine blood test reveals a high white blood cell count with increased numbers of immature white blood cells.

The approval of imatinib for treating the three phases of CML was based on three separate single-arm studies in about 1,000 patients who had failed conventional therapy. These clinical trials were not designed to determine whether imatinib improves survival. The sponsor is currently accruing patients for follow-up studies necessary to confirm clinical effectiveness of imatinib.

Side effects frequently reported in trials include nausea, vomiting, fluid retention, muscle cramps, skin rash, diarrhea, heartburn, and headache. Severe fluid retention occurred in up to 2 percent of patients, and any unexpected and rapid weight gain should be investigated and, if necessary, treated.

The drug is manufactured by Novartis Pharma AG for Novartis Pharmaceuticals Corp., East Hanover, N.J. Novartis began shipping the drug May 11.

Thompson said the two-and-a-half-month review time was "an all-time record for the evaluation of a highly complex, novel drug."

Members of the review team were:

- **Kimberly Benson, Ph.D.,** pharmacology and toxicology reviewer.
- **Gang Chen, Ph.D.,** statistics team leader.
- **Martin Cohen, M.D.,** medical reviewer.
- **John Duan, Ph.D.,** clinical pharmacology reviewer.
- **Joga Gobburu, Ph.D.,** pharmacokinetic consultant.
- **Sung Kim, Ph.D.,** chemistry reviewer.
- **John Leighton, Ph.D,** team leader, pharmacology and toxicology.
- **Richard Pazdur, M.D.,** director of the Division Oncology Drug Products.
- **Dotti Pease,** chief, project management staff.
- **Atik Rahman, Ph.D.,** team leader, clinical pharmacology.
- **Mark Rothmann, Ph.D.,** statistical reviewer.
- **Ann Staten, R.D.,** senior regulatory project manager.
- **Grant Williams, M.D.,** medical team leader.
- **Rebecca Wood, Ph.D.,** chemistry team leader.

Both CDER and NCI have Web sites devoted to imatinib at:

- *CDER:* http://www.fda.gov/cder/drug/infopage/gleevec/default.htm.
- *NCI:* http://newscenter.cancer.gov/pressreleases/gleevecpressrelease.html.

The Center's site contains the full product label.

Report to Nation Shows Balanced Programs

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activities in:

- Drug review.
- Drug safety and quality.
- International harmonization.
- Communications.

The report comes in versions for making a 48-page printout and for reading in an Internet browser. Slides of the charts are also available. The locations are:

- PDF: http://www.fda.gov/cder/reports/RTN2000/RTN2000.PDF.
- HTML: http://www.fda.gov/cder/reports/RTN2000/RTN2000.HTM.
- Slides: http://www.fda.gov/cder/reports/RTN2000/RTN2000.PPT.

See page 2 of this issue for information about printed copies.

Internal Reference Guide

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Parker (PARKERC, 7-7251) will make changes as you submit them. The last page of the guide is set up for submitting comments and revisions.

So, if you have questions about cell-mediated immunosuppressants or sweet spirit of nitre, consult the guide to find the subject matter expert.