news along the pike

JULY 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

VOLUME 10, ISSUE 2

INSIDE . . .

PIKE'S CORNERS . . .

FDA's 'Critical Path' report identifies research gaps

Drug development not keeping pace with basic discoveries

BY JANET WOODCOCK, M.D.

FDA's report, *Innovation or Stagnation?—Challenge and Opportunity on the Critical Path to New Medical Products,* provides our analysis of the "pipeline problem."

There is a slowdown—instead of an expected acceleration—in innovative medical therapies reaching patients. The medical product development path is becoming increasingly challenging, inefficient and costly.

As a consequence, our mission to ensure the availability of safe and effective medical treatments for Americans that take advantage of the latest science is becoming compromised.

In our view, the applied sciences for product development have failed to keep pace with the tremendous advances in the basic sciences. New science is not being used to guide the development process in the same way that it is accelerating the discovery process.

To focus the attention of the public, academic researchers, funding agencies and industry, our report identifies:

- The critical path for product development from design and discovery to commercial marketing.
- The scientific and technical dimensions of the critical path.
- The three types of research that support the critical path.

Critical path

An idealized "critical path" encompasses the development processes for drugs, biologics and devices. The critical path begins after basic research provides candidate products for development. These products then face successively more rigorous evaluation steps along the path, including:

- Prototype design or drug discovery.
- Preclinical development.

(Continued on page 10)

Regulatory Science, Review Enhancement projects

BY ROSA PEREZ

Regulatory Science and Review Enhancement projects are funded by the Center Director's Office and explore approaches, methods or data that could potentially enhance the quality or efficiency of the drug review process or the design and evaluation of clinical or non-clinical protocols.

Directions for submitting concept papers for new proposals or supplemental funding for current RSR projects are on CDER's intranet at http://cdernet.cder.fda.gov/ocd/rsr.htm.

The principal investigators for current RSR projects are presenting their research findings every third Tuesday at 1:30 p.m. The presentations began April 20 and will continue through the summer to Jan. 25.

Please join your colleagues in the Parklawn Building's Potomac Conference Room on the 3rd Floor. Each presentation will be for 20 minutes with 10 minutes for questions and answers.

(Continued on page 9)

CDER 2003 Report to the Nation available online, in print

BY NORMAN J. OLIVER

The Center's report on its performance for 2003 is now available in a printed version as well as on the Internet. The report has 1995-2003 performance statistics, program descriptions and major initiatives. While they last, you can pick up printed copies from the Medical Library and its branches or from OTCOM in Parklawn Room 12B-31.

If you're not in Parklawn Building, you can send me an e-mail at olivern@cder.fda.gov for delivery by mail or distribution.

Online versions and slides of the charts and graphs are available on CDER's Website at:

- **PDF:** http://www.fda.gov/cder/reports/rtn/2003/rtn2003.pdf.
- **HTML:** http://www.fda.gov/cder/reports/rtn/2003/rtn2003.htm.
- **Slides:** http://www.fda.gov/cder/reports/rtn/2003/rtn2003.ppt.

JOE'S NOTEBOOK

Cancer death rates, incidence decline

The nation's leading cancer organizations have reported that Americans' risk of getting and dying from cancer continues to decline. Also, survival rates for many cancers continue to improve. The *Annual Report to the Nation on the Status of Cancer, 1975-2001* finds that death rates from all cancers combined dropped 1.1 percent per year from 1993 to 2001. The overall observed cancer incidence rates, or the frequency with which cancer occurs, dropped 0.5 percent per year from 1991 to 2001. The new data reflect progress in prevention, early detection and treatment; however, not all segments of the U.S. population have benefited equally from the advances.

First issued in 1998, the report is a collaboration among the American Cancer Society, the Centers for Disease Control and Prevention, the National Cancer Institute and the North American Association of Central Cancer Registries. It provides updated information on cancer rates and trends in the United States and features a special section on cancer survival.

Death rates decreased for 11 of the top 15 cancers in men and eight of the top 15 cancers in women. Lung cancer death rates among women leveled off for the first time between 1995 and 2001, after continuously increasing for many decades.

Cancer incidence rates among men, have recently declined for seven of the top 15 cancer sites: lung, colon, oral cavity, leukemia, stomach, pancreas and larynx. Incidence rates in men increased for melanoma and cancers of the prostate, kidney and esophagus.

For the first time, lung cancer incidence rates among women are on the decline. Incidence rates decreased for five additional cancers out of the top 15 in women: colon, cervix, pancreas, ovary and oral cavity. Breast, thyroid, bladder and kidney cancer, and melanoma rates are rising among women.

Survival improvements noted

The report highlights trends in cancer survival by comparing five-year survival rates of cancer patients diagnosed in two time periods: 1975-1979 and 1995-2000. Between those time periods, survival substantially improved for most of the top 15 cancers in both men and women as well as the top 10 sites in children.

For men, large gains in cancer survival rates (more than 10 percent) were seen in cancers of the prostate, colon and kidney and non-Hodgkin lymphoma, melanoma and leukemia. Modest gains (5 percent to 10 percent) were found for cancers of the bladder, stomach, liver, brain and esophagus.

For women, large gains in cancer survival rates were seen for colon, kidney and breast cancers and non-Hodgkin lymphoma. Modest gains were found for bladder, oral cavity, stomach, brain, esophageal and ovarian cancers and melanoma and leukemia.

Limited survival improvement was noted for the most fatal forms of cancer in adults including cancers of the lung, pancreas and liver, which are characterized by late stage at diagnosis and relatively poor survival rates even when these cancers are diagnosed at a localized stage. There was also little or no gain in several cancers that already have high survival rates, including larynx, thyroid and uterine cancers.

Childhood cancers showed some of the largest improvements in cancer survival during the past 20 years, with an absolute survival rate increase of 20 percent in boys and 13 percent in girls. The current five-year survival rate of more than 75 percent confirms substantial progress made since the early 1960s, when childhood cancers were nearly always fatal.

The report is available online at http://www.seer.cancer.gov. Click on the icon "1975-2001 Report to the Nation."

news along the pike

The Pike is published electronically approximately monthly 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:

NEWS ALONG THE PIKE
CDER Office of Training
and Communications (HFD-210)
Parklawn Building, Room 12B-31

Editor: Norman "Joe" Oliver (OLIVERN)
Associate Editors: Patrick Clarke,
Christine Parker
Phone: (301) 827-1695
Fax: (301) 827-3055

Dr. Seligman works with CERTs to optimize use of therapeutics

By Patrick E. Clarke

CDER's **Paul Seligman, M.D.,** is one of two FDA members on the steering committee for the Centers for Education and Research on Therapeutics. Dr. Seligman is the director of CDER's Office of Pharmacoepidemiology and Statistical Sciences. The other current FDA representative on the steering committee is **Susan Gardner, Ph.D.,** from the Center for Devices and Radiological Health.

CERTs, administered by the Agency for Healthcare Research and Quality in consultation with FDA and other HHS agencies, is composed of seven academic centers. The research agenda is led by the national steering committee that includes representative leaders in health care, public health, government and industry.

"CERTs continues to have broad representation on the steering committee from FDA, as CDER, CBER and CDRH have been represented," Dr. Seligman said.

The steering committee works to shape and support the CERTs mission to conduct research and provide education in order to advance the optimal use of drugs, medical devices and biological products.

Over the past two years CERTs has sponsored a series of multi-disciplinary workshops, called the Risk Series, focusing on risk communication, risk management, benefit assessment and working with the media. Each workshop included 45 to 50 invitees representing government agencies, medical and professional societies, universities, pharmaceutical companies and consumers.

"The idea was to talk about key issues and to identify gaps or areas where further research is needed. A number of publications, some still in press, have been generated by this series—and recommendations from the series can serve as a guide as to where research resources should go," Dr. Seligman said.

At a recent quarterly CERTs steering committee meeting, the discussion was focused on a series of strategic initiatives planned by the organization, Dr. Seligman said.

Among the top CERTs strategic initiatives that were identified during the meeting were:

- Following up on the Risk Series recommendations.
- Examining the impact of the Medicare Modernization Act and its implications on the availability of medications and possible risks and benefits of the new law.
- Continuing to focus on improving the safety of marketed therapeutics, including consideration for developing a national problem list of therapeutics.
- Improving the on-going educational progress and curriculum development for health care providers and recognizing that doctors and pharmacists play a critical role in the risk-benefit equation.
- Evaluating the impact of computerized physician order entry systems, where rather than writing a prescription, the doctor just enters it right into a computer.

"All the initiatives fit very nicely into FDA's strategic initiatives and are supportive of what we're trying to do at an Agency level," Dr. Seligman said. "With computerized physician order entry systems being increasingly used in hospitals and in-patient settings, it is vital to understand how well they are being accepted and used, and whether we are realizing their potential to reduce medical errors.

"As we continue to strive to improve the quality of health care by improving the safe use of all medical products, I expect that the CERTs will play an increasing role in defining best practices and assessing the impact of risk management efforts, regulatory guidance and legislation on quality."

OGD lists Paragraph IV application dates

CDER's Office of Generic Drugs has begun providing more information to the public to help generic drug applicants determine if they are eligible for 180-day marketing exclusivity for their products.

In response to two citizen petitions, the OGD Web site will disclose the submission date for the first substantially complete generic drug application containing a challenge to a patent listed for the innovator drug. Application with this "Paragraph IV" patent certification could be eligible for 180 days of marketing exclusivity if approved and the patent challenge is upheld.

This 180-day marketing exclusivity is an effective incentive for generic drug development provided under the Hatch-Waxman Amendments to the Federal Food Drug and Cosmetic Act.

The list includes the name of the drug product, dosage form, strength (subject of Paragraph IV certification), reference listed drug and the date on which the first substantially complete generic drug application was submitted. FDA will not disclose the identity of the applicant.

By displaying the submission date along with the trade and generic name of the drug, its dosage form, and the strengths of the drug products, the Agency will provide a fairer, more transparent way for all interested parties to gain access to this information. With better, more transparent information, generic manufacturers will be able to plan their development of additional generic products more effectively. The list can be found at http://www.fda.gov/cder/ogd/ppiv.htm.

Pike's Puzzler

Medical scramble

By Tony Chite, P.D.

Unscramble the letters below to spell a medical term:

1. **S A I M A N E**
2. **M A R G O O N S**
3. **R E G O I T V**
4. **U S E A A N**
5. **V U J C C I I I S T T O N N**
6. **S H A R**
7. **M O R T E R**

Key: 1. amnesia; 2. sonogram; 3. vertigo; 4. nausea; 5. conjunctivitis; 6. rash; 7. tremor

Tony Chite is a pharmacist and CSO with the Division of Information Disclosure Policy.

CDER launches new easy-to-use drug information Web site

By Monica Unger

Drugs@FDA is the first publicly available Internet resource to offer a comprehensive overview of a drug product's approval history.

As part of FDA's continuing efforts to see that patients and consumers have the information they need to make informed choices, the searchable database includes information on approved prescription drugs, some over-the-counter drugs and discontinued drugs.

Drugs@FDA makes all drug approval information available on one site so that you no longer have to visit several CDER Web pages for information on brand-name and generic drugs.

The database incorporates information from other parts of CDER's Web site, including consumer information sheets, medication guides, labeling and other information for patients. Eventually information on recalls, warnings and drug shortages will also be included.

You can easily search or browse this site by drug name or active ingredient to retrieve a complete approval history and accompanying documents for a particular drug product. For many drugs approved in 1998 or later, these documents include the approval letter, labeling and reviews.

You can also find out if therapeutic equivalents exist including generics for brand-name drugs.

Drugs@FDA can be used in other ways. For example, you can:

- Get the latest FDA information, including consumer-focused information like Medication Guides, for drugs you have been prescribed or that your doctor is considering.
- Identify therapeutically equivalent drugs for prescription medicines
- Identify alternative OTC drugs with the same active ingredient.
- Determine whether generic equivalents exist for a brand-name drug.

You can access the site by clicking on Drugs@FDA under Quick Info Links on the top right on CDER's home page (http://www.fda.gov/cder/).

The Division of Library and Information Services in the Office of Training and Communications developed Drugs@FDA. The developers were **Paul Stauffer, Sally Winthrop, Bill Woodard** and I, under guidance from **Carol Cavanaugh,** the division director. A contractor provided programming services for the project. We would very much like to hear from you as you use the site. You can send us feedback by clicking on the "Contact Us" link at the top of the Drugs@FDA home page.

Monica Unger is the project manager for Drugs@FDA.

Crime prevention seminar emphasizes personal safety, security

By Patrick E. Clarke

The Program Support Center sponsored a Crime Prevention Seminar on May 11. Members from the Department of Health and Human Services Federal Protective Service conducted the program.

"Preventing crime starts with you," said **Mary E. Brown,** a physical security specialist. "Know what's going on around you, be aware of your surroundings."

She also emphasized the need to challenge people you are not familiar with—not in an aggressive manner—but just with a simple, "Can I help you?"

Brown pointed out that women often don't lock their purses in their desks when they leave their offices—and they should. "And I've seen too many people who wear their best jewelry to work. That's just not a good idea," she said.

David Hall, chief of security at Parklawn, stressed that the guards should be called first regarding any incident at (301) 443-4144. Then it can be determined if FPS is to be called.

James Ward, physical security specialist, then took the podium. "If you don't get anything else out of this seminar, take down our phone number – 202 708-1111," Ward said.

Ward pointed out that not only valuables, but information can be stolen. So, be sure to log off your computers when leaving the workplace for extended periods of time.

He also suggested keeping your personal keys locked up during the workday and carrying your office keys on a separate ring. "And never mark your keys with a label," Ward said. "Identify your keys by a distinctive key ring."

Ward also explained the concept of crime prevention through environmental design. "For example, if your coat rack is near to a door, move it to another location because it's too easy for a coat to be snatched if it's near a door," Ward said.

"Another example is if you work in cubicles, make sure at least two workstations are in a position where employees can monitor entrances and exits," Ward said.

The seminar concluded with a bomb-detection demonstration by K-9 Susie, a golden retriever, and one of 23 sniffer dogs in FPS.

Frequently asked questions about OTC drugs on Web

By Ron Wilson

Small pharmaceutical businesses now have a resource for questions about the over-the-counter drug review process. OTC drugs and the OTC review drug process are a major interest of small pharmaceutical businesses.

David Hilfiker of the Division OTC Drug Products and **Mitch Weitzman** of the Office of Regulatory Policy worked with OTCOM's Small Business Assistance to develop a Q&A document on OTC Drugs that provides basic definitions to OTC terms and information about marketing an OTC drug product.

The document helps explain basic questions about the different routes to OTC marketing: monograph, time-and-extent application, Rx-to-OTC Switch or new or generic drug application.

This will not only be helpful to small pharmaceutical businesses but other stakeholders who are unfamiliar with the OTC drug process. The resource can be found on the Small Business Web site at http://www.fda.gov/cder/about/smallbiz/default.htm.

Ron Wilson heads CDER's Small Business Assistance in OTCOM.

Office of New Drug Chemistry director has mandate for change

By Patrick E. Clarke

The Office of New Drug Chemistry is scheduled to move to the White Oak campus in 2005 and anticipates a reorganization as well.

"I'm hoping that we will have a new organizational structure to support the new, reengineered chemistry, manufacturing and control review practices by then," said **Moheb Nasr, Ph.D.,** ONDC's permanent director. Dr. Nasr had served as acting director for six months, however, and has some clear mandates and an expectation for change within the office.

"Quality Management System is a systems approach that will be integrated gradually into the chemistry, manufacturing and controls review functions," Dr. Nasr said. The FDA Management Council has endorsed the quality document drafted by the Good Manufacturing Practices Steering Committee, according to Dr. Nasr.

"We'll be starting with question-based, CMC peer reviews. When the review is completed by ONDC reviewing scientists, a presentation will be made for representative drug applications before CDER scientists. The focus will be to evaluate the quality of the review, to provide input on the critical aspects of the review and to learn how to utilize risk-benefit-analysis in CMC review," Dr. Nasr said.

As the feedback will be coming from peers, it's expected that it will be received more positively. "We've already started this program and we have a plan for the rest of the year," Dr. Nasr said.

In addition to quality systems, Dr. Nasr anticipates that input into reengineering the CMC review function will come in part as a result of consultations with regulatory bodies.

"I'll be discussing ONDC review practices with other regulatory agencies throughout the world," Dr. Nasr said. He met with Canadian officials in March and was on extended travel throughout Europe to discuss and evaluate their CMC review practices.

"We are trying to focus our resources on the review of critical aspects of CMC submissions rather than reviewing everything in the drug application. The idea is to achieve timely, high-quality science and risk-based CMC reviews within our existing resources," Dr. Nasr said.

Dr. Nasr also will be looking to add personnel to the 125 chemists and pharmaceutical scientists he is currently responsible for. "Recruiting is a key area for this office. We're looking for industrial pharmacists, pharmaceutical engineers, analytical chemists and specialists in special dosage forms and delivery systems—areas where we need more expertise," Dr. Nasr said.

The problem with making some of the changes Dr. Nasr envisions is a very heavy workload. "We deal with about 1,700 supplemental NDAs a year in addition to NDAs, INDs and industry meetings. The workload keeps increasing every time a new application is approved while our resources don't increase. We either get more resources, change the way we do business or both," Dr. Nasr said.

As a former professor and chemistry department chair at Lindenwood University in St. Charles, Mo., Dr. Nasr is a strong advocate for research. "I think integrating more research into our reviews is critical and helps our reviewers stay at the cutting edge of science. In fact, I don't think we provide enough research opportunities and professional development to assist our reviewing scientists in career development," Dr. Nasr said.

Ultimately, Dr. Nasr would "Like to change the way we conduct CMC review in ONDC to improve the quality of the work environment."

Dr. Nasr's management style is a combination of direct involvement and delegation. "I like to be hands-on in addressing science and research issues, but I also rely on our senior staff that have more regulatory experience than I do," Dr. Nasr said.

"And I take a personal interest in every staff member. I feel responsible for addressing everyone's needs, so my door is always open," Dr. Nasr said.

Dr. Nasr began working with the federal government in 1989 as a science advisor for the Division of Drug Analysis, which later became the Division of Testing and Applied Analytical Development DTAAD. He took a full-time position with DTAAD as a research chemist in 1991.

Dr. Nasr obtained his bachelor of science degree in pharmacy and his master of science in pharmaceutical analysis from the University of Cairo's College of Pharmacy in Egypt and his doctorate in chemistry from the University of Minnesota in Minneapolis. He has been the co-investigator and co-author of over 35 major research studies.

CDER employees enjoy picnic weather, tour White Oak grounds, buildings

Center employees attended a celebration of CDER at the new White Oak campus on the afternoon of May 12. Warm weather greeted picnickers who had an opportunity to socialize and try several games.

A highlight was the opportunity to tour the Center's office space while it was still under construction. Many also toured the completed Life Sciences Building that houses the Office of Testing and Research's laboratories.

The official committee for the event consisted of:

- Office of Executive Programs: **Tanya L. Abbott, Deborah J. Henderson** (chair)**, Justina A. Molzon, Vikki S. Kinsey.**
- Office of Management: **Eileen Cole.**
- Office of New Drugs: **Rene Kimzey, Sandra L. Kweder, Barbara J. Townsend.**
- Office of Pharmaceutical Science: **Ted M. Sherwood.**
- Office of Pharmacoepidemiology and Statistical Science: **Ruth Davi, Cyndy Kornegay, Martha O'Connor.**
- Office of Training and Communications: **John Friel, Nancy D. Smith.**

"However, there were a number of very busy subcommittees and a multitude of other individuals who made the event happen, including some who actually contributed more than some of the committee members," Debbie Henderson said.

You can see photos of the new facilities and construction progress at on FDA's intranet at http://intranet.fda.gov/ofacs/white_oak.

Spring retreat focuses on current scientific, regulatory issues

BY GARY P. BOND, PH.D., DABT

The semiannual scientific retreat for CDER's pharmacology and toxicology reviewers, held May 27, focused on screening INDs, phospholipidosis, evaluating the abuse potential of drugs in development, 505(b)(2) applications, product labeling, routes of administration and an update of activities (page 9) from the Office of New Drugs.

David Jacobson-Kram, Ph.D., DABT, OND's associate director for pharmacology and toxicology, shared a brief overview of screening INDs, which aim at facilitating the drug development screening process at the front end, prior to more extensive, time-consuming and expensive non-clinical and clinical testing. He discussed the microdose IND, exploratory IND and facilitated IND.

The keynote address, "Phospholipidosis: Why are we interested?" was presented by **Lawrence F. Sancilio, Ph.D.**, of the Division of Pulmonary and Allergy Drug Products. Phospholipidosis is a condition in which there is an excess accumulation of fatty molecules called phospholipids in tissues due to alteration of their synthesis and/or metabolism.

This is seen in the fatal Niemann-Pick disease in children and with toxicity associated with phospholipidosis-inducing drugs. A working group has been established to determine from the FDA compound database whether there is a direct correlation between phospholipidosis and clinical toxicity. This is an area that is of great interest both to the FDA and to the pharmaceutical Industry.

Evaluating drug abuse potential

Katherine Bonson, Ph.D., from CDER's Controlled Substance Staff, discussed how drugs are assessed for abuse potential during the drug development process. When an NDA is submitted, both the Food, Drug and Cosmetic Act and the Controlled Substances Act require an abuse potential assessment. In evaluating whether a drug is likely to be abused, biochemical and behavioral data from animals and humans are reviewed, which may lead to a recommendation for scheduling under the Controlled Substances Act. Review divisions can consult with the Controlled Substance Staff at any time during the IND or NDA review of a drug with central nervous system activity.

505(b)(2) applications

Chuck Resnick, Ph.D., Division of Cardio-Renal Drug Products, discussed the reason for this route to approval for a new drug and our review responsibilities. The 505(b)(2) application allows sponsors who do not have a right of reference to all the data needed for an approval to rely on the Agency's findings of safety and efficacy for an approved drug or on published literature, rather than conduct their own studies.

These applications differ from generic drug applications, which can only be approved for drugs identical to a reference listed drug in terms of active ingredient, bioavailability and conditions of use, or for drugs that differ from a reference listed drug in ways that do not require additional clinical studies (other than bioequivalence) to establish safety and efficacy.

The 505(b)(2) applications can be approved for drugs that differ from an approved drug in ways that do require additional clinical trials. Dr. Resnick discussed several other issues with these applications including patent exclusivity and submission data requirements.

Guidance on writing product labeling

Jeri El-Hage, Ph.D., Division of Metabolic and Endocrine Drug Products, reviewed the specific requirements on content and format of labeling for human prescription drugs. She emphasized that we should carefully review statements about the mechanism of action and receptor selectivity in the clinical pharmacology section because this information is generally derived from non-clinical pharmacology studies and is often used to make marketing claims.

She discussed recommendations for writing an animal pharmacology section for drugs approved under the Animal Efficacy Rule (Subpart H) and an animal toxicology section for toxicities observed in animals but not clinically monitorable, such as drug-induced vasculitis and central or peripheral neuropathy.

Dr. El-Hage referred reviewers to the regulations, examples of approved labels for the particular issues such as boxed warnings based on toxicity data and other CDER resources for consultation. She discussed the guidance on the specific information such as doses studied that should be provided to improve consistency in the non-clinical labeling sections.

Routes of administration

Inhalation studies and non-clinical safety assessments. I shared the special considerations that are part of safety assessments for inhaled drugs. Among several important considerations, most notable is particle size of the inhaled drug, which determines the amount of pulmonary deposition and, hence, the actual dose of a drug. Pulmonary deposition factors differ among species and must be considered in identifying the actual doses for the No Observed Adverse Effect Level. These NOAELs are used to determine safety margins for proposed doses in clinical trials and whether studies in humans are considered safe to proceed based on non-clinical study data.

Laryngeal squamous metaplasia in rats in inhalation studies. **Luqi Pei, Ph.D.,** Division of Pulmonary and Allergy Drug Products, discussed the interpretation of laryngeal squamous metaplasia in rats. This is a common pathological finding in inhalation toxicity studies in the species. The phenomenon appears to be an adaptive, protective and species-specific response in rats. In most cases, it carries little relevance in the non-clinical safety evaluation of inhalation drug products in humans. The presentation was informative to reviewers who do not routinely evaluate inhalation toxicity studies now, but are expected to review more of such studies in the future as the inhalation route of administration gains popularity in drug development.

Non-clinical studies for drugs administered by the ocular route. **Zhou Chen, Ph.D.,** Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, presented an overview of the specifics for non-clinical studies required for ophthalmic drugs. He explained eye structure and different ocular dosing routes. The need

(Continued on page 7)

Pharm/tox retreat tackles issues in non-clinical safety assessment

(Continued from page 6)

for certain ocular toxicity data determines the type of animal studies that need to be performed.

Dr. Chen addressed animal species selection and ocular toxicity evaluation. He also discussed ophthalmic drug formulation, dosing frequency, dosing volume and study duration in ocular toxicity study design. While most ocular drugs are applied to the eye, several drugs given orally may have intended and unintended ocular effects.

Non-clinical safety assessments for intrathecal drug products. **Dan Mellon, Ph.D.,** Division of Anesthetic, Critical Care and Addiction Drug Products, explained the differences between epidural, intrathecal and intraspinal dosing and associated relative absorption rates and effectiveness. Although there are a number of drugs that have been approved for epidural administration, there are only a few drugs that have been approved by FDA for intrathecal use. Intrathecal drugs are injected directly into the spinal cord rather that epidurally into the fluid surrounding the spinal cord.

Due to the sensitivity of the neurons in the spinal column, the non-clinical safety assessment for drugs seeking an epidural indication should characterize the inadvertent administration of the drug product into the intrathecal space. The non-clinical safety assessment for drugs seeking a chronic epidural or intrathecal route of administration has been limited by a the availability of adequate animal models. Dr. Mellon also presented an example of clinical studies inappropriately preceding adequate non-clinical assessment.

The retreat started with opening remarks from **Hanan Ghantous, Ph.D., DABT,** the chairperson of the meeting, followed by true-false questions about FDA's future home, White Oak. One of the true statements was that, in 1995, an explosive storage magazine exploded, causing limited damage to some of the surrounding communities. Reviewers living close to White Oak remember hearing the explosion.

The retreat was organized by pharm/tox reviewers and staff from various divisions including Dr. Ghantous (chair), **Margot Brower, Ph.D., Dave Hawver, Ph.D., Steve Kunder, Ph.D., Shwu-Luan Lee, Ph.D., Yanli Ouyang, Ph.D., DABT, Tom Papoian, Ph.D., DABT, Adele Seifried, Suzanne Thornton-Jones, Ph.D.,** and myself.

Gary Bond, a senior staff fellow in the Division of Pulmonary and Allergy Drug Products, acknowledges the assistance of the speakers and retreat committee members in preparing these articles.

Dr. Jenkins provides pharm/tox retreat with update on Office of New Drugs

BY GARY P. BOND, PH.D., DABT

During the scientific retreat for pharm/tox reviewers, **John Jenkins, M.D.,** the director of the Office of New Drugs, talked about:

- The White Oak move.
- The OND reorganization
- ODE associate directors for pharmacology and toxicology.
- The quality systems approach to processes and procedures
- The Critical Path Initiative.
- Screening INDs.

White Oak move

This will take place by about May of next year. The move will provide an opportunity for revitalization, culture change and consolidation of all our colleagues and resources in a new facility in a community that is excited about our arrival.

OND reorganization

No major changes are envisioned. The reorganization will happen in a way that creates logical groupings in the same divisions, creates divisions with better balanced workloads and resource allocation, and completes the integration of biologics reviewers and indications into CDER.

ODE pharm/tox associate directors

These new positions form a critical part of the pharm/tox discipline. The associate directors will emphasize such things as education, recruitment, reviewer training and consistency of reviews through tertiary reviews.

[Earlier during the retreat, **Ken Hastings, Ph.D., DABT,** the associate pharm/tox director for ODEs II and III, had introduced **Abby Jacobs, Ph.D.,** the associate pharm/tox director for ODEs IV and V, and **David Green, Ph.D.,** the associate pharm/tox director for ODEs I and VI. Dr. Hastings had also described the facilitator roles expected of the associate directors.]

Dr. Jenkins emphasized that he expects everyone to support the associate directors in their important support function to OND. In response to another question related to the associate director function, he noted that the tertiary review of genotoxicity and carcinogenicity reviews creates consistency and harmonization of OND's recommendations and decisions to the industry and the public, especially when the decisions involve clinical holds.

Quality systems

This is a dynamic, transparent approach to processes and procedures that defines staff function and accountability and the mechanisms for improvement. Outside contractors have done the systems assessment. Implementation of the recommendations will be forthcoming. This is a good thing, Dr. Jenkins asserted.

Critical Path Initiative

Janet Woodcock, M.D., acting deputy commissioner for operations, has been very involved in this activity (page 1). The initiative aims at promoting public health by facilitating development of safe, effective drugs and increasing public awareness of FDA's role in transitional and critical path research that moves drugs along from basic research to and through the development process.

Screening INDs

These (page 8) are still in policy development by OND and are an important project in the critical path initiative. Dr. Jenkins is considering the feasibility of a separate review group for screening INDs, either dedicated or *ad hoc,* depending on the workload.

Budget

In response to a question, Dr. Jenkins noted that the budget is tight and will be tight, or at least flat. He said that there are currently no hiring freezes on scientific staff; however, staff ceilings must be managed.

Compliance's Therapeutics Facilities Review Branch keeps pace

BY PATRICK E. CLARKE

'We haven't missed a PDUFA date since I have been here," said **Michael Smedley,** branch chief of the Therapeutics Facilities Review Branch, Division of Manufacturing and Product Quality, which is in CDER's Office of Compliance. While Smedley is proud to be able to make that statement, working long hours to keep up has become commonplace in the branch. "This group is running at 200 percent, and we're ready to go to 100 percent," he said.

The branch, consisting of eight people, was part of the transfer of therapeutic biologics to CDER in October 2003. In December, Smedley came from the Center for Veterinary Medicine to serve as acting branch chief and has been permanently selected for the position.

"Shortly before I started, four senior reviewers/investigators went back to CBER," Smedley said. "We ended up with two senior reviewers who were both part-time employees, and two who still needed inspection training." Since then, one of that group has left the federal government.

"We've had numerous employees come from within our own Division of Manufacturing Product Quality in the Office of Compliance for details and one from the Office of Biotechnology Products," Smedley said. "The detailees have been invaluable and have helped keep us afloat, but it takes a while for them to learn our processes. They generally get productive toward the end of their 60-day detail."

The branch's members have responsibilities in the following areas:

- Application review of transferred therapeutic products.
- Pre-submittal support for meetings with industry.
- Review of chemistry, manufacturing and controls and establishment description.
- Serving as facility inspection team leaders.
- Consulting on premarket reviews and ensuring compliance with current good manufacturing practices after approval.
- Providing support functions, including policy and guidance document development; cGMP and inspection training; and industry presentations.

The work done by the branch is comprehensive, complex and requires a good scientific understanding of the process. The branch reviews the portion of the biologic license application or supplement that deals with a facility. If a pre-approval inspection for a BLA is needed, it is performed by one of the branch's reviewer-investigators as the lead investigator. The reviewer's tasks include review of equipment, floor diagrams and classifications, environmental assessments, the method of manufacture and packaging and an entire section of checks regarding microbiology.

The Microbiology Section includes review of drug product solution filtration, specifications concerning hold times, critical aseptic operations, sterilization processes, depyrogenation processes, aseptic process validation, environmental monitoring, product component bioburden. "Many of the CMC review responsibilities are shared with the product office reviewer, Smedley said. "For example, for the container/closure system we focus on integrity and biocompatability studies while the product office review stability of the drug substance in the container."

Sometimes, a supplement to an application can require almost as much work as an original application. "A prior approval supplement could require multiple inspections, plus all the paperwork, such as writing the inspection reports and review of the submitted application. And companies are constantly supplementing," Smedley said.

During a prior-approval inspection, the reviewer becomes an investigator and covers the following facility related issues such as manufacturer identification, floor diagrams, other products in multi-product areas, raw materials and reagents, manufacturing flow charts, animal facility cGMP issue and in-process controls, Smedley said.

The branch previously had regulatory project managers to help coordinate the workload. "But our branch hasn't had any RPMs since the move to CDER," Smedley said. "We have scientists doing RPM work. It's just not efficient."

The branch also didn't have a secretary until recently. "We do have a secretary now for two days a week; although, we share the secretary with another branch," Smedley said. "Employees have been working long hours and haven't been taking their vacations."

Smedley's own schedule has been brutal. "Often, the review part of my day starts after 5 p.m., after reviewers have turned in their submissions. I'm here for 4 to 5 hours after that. So, 12- to 14-hour days haven't been uncommon. Now that we have eight permanent reviewers in the TFRB, things are starting to get back to normal," Smedley said.

"The Therapeutics Facilities Review Branch has survived the transition from CBER to CDER. We have been able to put together a highly qualified staff that is in the process of integrating all aspects of their review and inspection process into CDER. These individuals bring with them, strong educational, industrial, scientific and FDA backgrounds. The TFRB reviewers have all done an exceptional job."

"But it takes about a year to train a reviewer and possible two to three years to train as an investigator, depending on the employees background," Smedley said. "If the INDs that are out there now turn into BLAs we could easily be swamped. We don't know if next year we'll get 5 or 70 new ones."

Smedley hopes the branch will grow in both efficiency and personnel.

"For the future, we plan to add efficiencies to the process and in line with the cGMPs for the 21st Century Initiative will bring the best science to our reviews and inspections," Smedley said. "This growing segment of the pharmaceutical industry will benefit and be able to use the latest technologies for manufacturing, risked-based approaches and continuously improve. We hope to continue to grow beyond just one new employee but at least at a pace to keep up with the exponential growth possible with the biotech industry."

Regulatory Science Review Enhancement projects to be presented

(Continued from page 1)

The schedule, the project titles and principal investigators are:

April 20

"Estimating the background rates of joint symptoms/conditions in the pediatric population," **Eileen Navarro.**

"Disseminating new CDER safety information: evaluation of the effectiveness of MedWatch—e-mail notification to pharmacy healthcare professionals," **Norman S. Marks.**

June 15

"Application of classification and regression tree (CART) statistical models for the identification of clinical factors associated with drug-specific adverse events," **Allen Brinker.**

"Statistical issues in design and analysis of drug abuse study," **Yi Tsong.**

July 20

"Evaluation of the effect of demographic factors on the QT interval and modeling of baseline variations in the QT Interval on QT altering drugs," **Sam Haidar.** *(cancelled)*

"Evaluation of the time-course of drug effect on QTc interval and the implications of delayed response on the correlation between drug concentration and QT prolongation," **Sam Haidar.** *(cancelled)*

"Flexible designs for clinical studies," **James Hung.**

August 17

"Population approach in drug development and review process: Study design and execution, data analysis, results reporting, and the impact on labeling—survey-based FDA experience and future recommendations," **He Sun.**

"Dosing of methylphenidate in attention deficit hyperactivity disorder (ADHD) in children based upon pharmacokinetic/pharmacodynamic (PK/PD) modeling incorporating effects of tolerance, body size, formulation, and food via trial simulation," **Ronald Kavanagh.**

"A systematic approach to improve methods of hepatic impairment," **Vanitha Sekar.**

September 21

"Proper dosage adjustment in subpopulations," **He Sun.**

"Requirement of adults-to-children bridging studies," **He Sun.**

"Development of an Integrated *in vitro/in vivo* PK/PD model for HIV therapy: Prediction of the potential benefit of subtherapeutic ritonavir dose as a pharmacokinetic boosting agent for other HIV protease inhibitors," **Jenny H. Zheng.**

October 19

"Standardization of liposomal drug product quality," **Brian Booth.**

"Evaluation of hypotheses-driven methods for functional genomic oncology studies," **Ning Li.**

"Design and power consideration of pharmacogenomics studies," **Sue-Jane Wang.**

November 16

"Determination of the time to onset of therapeutic response for psychiatric drugs," **Robert Levin.**

"Evaluating biomarkers as surrogate endpoints using sensitivity and specificity analyses," **Rajeshwari Sridhara.**

December 21

"The impact of risk management programs on the practice of pharmacy," **Lauren Lee.**

"Identification of immunotoxic drugs using standard non-clinical toxicology studies," **Lynnda Reid.**

"Utility of multiple event time analysis methods for evaluation of drug safety and efficacy in new drug applications," **Sue-Jane Wang.**

January 25

"Screening clinical drug-drug interactions using population pharmacokinetic approach," **He Sun.**

"Criteria used in the Approval of Alternate Modes of Administration of Oral Dosage Forms in Special Populations i.e., Pediatric and Elderly Patients," **Suresh Doddapaneni.**

"Optimization of dosage regimen based on assessment of toxicity and synergism of efficacy of irinotecan hydrochloride (CPT-11) and 5-fluorouracil/leucovorin with population PK/PD Modeling," **John Duan.**

Rosa Perez is the RSR project manager in the Office of Executive Programs.

1st step taken to recognize role of emerging manufacturing technologies

In March, FDA revised a long-standing policy document regarding the validation of pharmaceutical manufacturing processes for drugs that are subject to pre-market approval requirements.

This is an important first step in the Agency's plan to address the area of process validation. The effort is being taken in concert with FDA's initiative on the regulation of pharmaceutical quality known as "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach."

New to this version are:

- Recognition of the role of emerging advanced engineering principles and control technologies in ensuring batch quality. For drugs produced using these new principles and technologies, this guidance provides for possible exceptions to the need for manufacturing multiple conformance batches prior to initial marketing.
- Deletion of the previous reference to "three" validation (or conformance) batches at commercial scale as adequate minimum proof of process validity—a number is no longer suggested.
- Further clarification of the importance of post-market information gathering especially for those batches released to market concurrent with the manufacture of the initial conformance batches.

As with the previous version, the new version reaffirms that Agency drug product pre-market review units may approve applications for marketing before a firm has manufactured one or more conformance batches at commercial scale, also sometimes referred to as "validation" batches.

The revised guidance again recognizes certain conditions under which a firm may market batches of drugs while gathering data to confirm the validity of the manufacturing process.

More information is available on CDER's Web site at http://www.fda.gov/cder/gmp/processvalidation.htm.

Critical Path report calls for modernizing development tools

(Continued from page 1)

- Clinical development.
- FDA filing/approval and launch preparation.

A striking feature of this path is the difficulty, at any point, of predicting ultimate success with a novel candidate. Recent biomedical research breakthroughs have not improved our ability to identify successful candidates.

Critical path dimensions

From the earliest phases of preclinical work to commercialization, developers must manage in these three dimensions:

- *Assessing safety*—showing that a product is adequately safe for each stage of development.
- *Demonstrating medical utility*—showing a new product will actually benefit people.
- *Industrialization*—turning a laboratory concept into a consistent and well-characterized medical product that can be mass produced.

The traditional tools used to assess product safety—animal toxicology and outcomes from human studies—have changed little over many decades and have largely not benefited from recent gains in scientific knowledge.

Better tools are needed to identify products that will prove clinically useful and eliminate impending failures more efficiently and earlier in the development process.

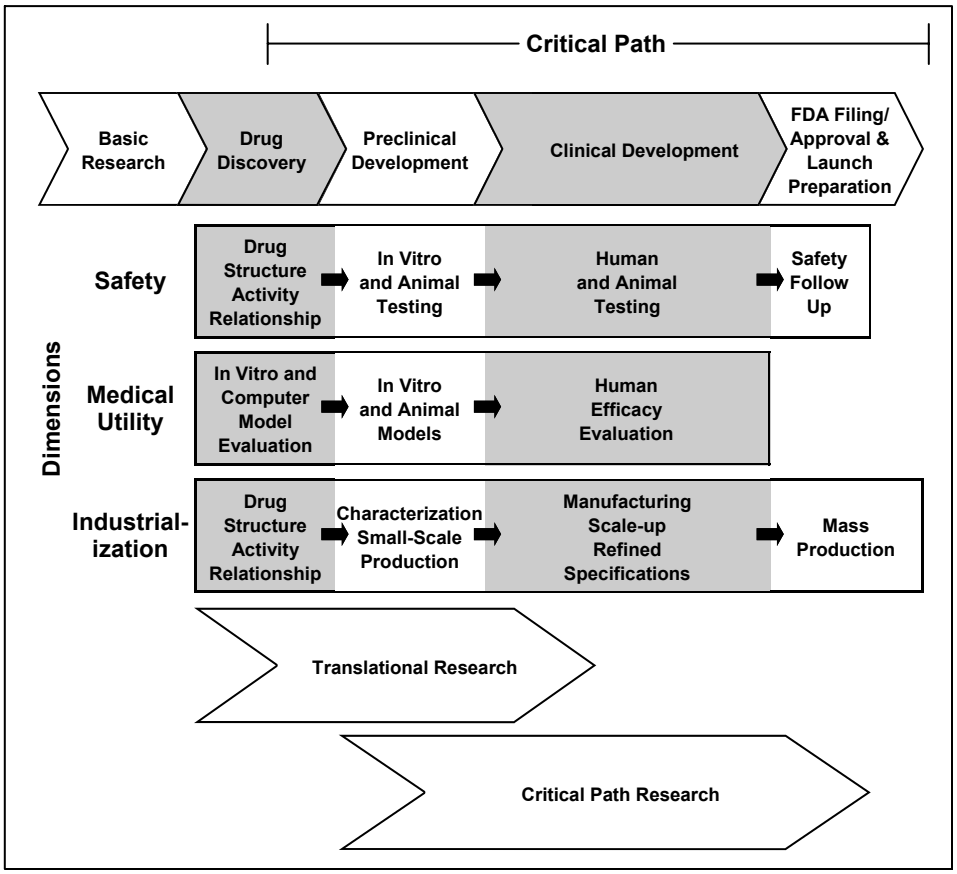
The current drug discovery process, based on in-vitro screening techniques and animal models of often poorly understood clinical relevance, is fundamentally unable to identify candidates with a high probability of effectiveness. Reaching a more systemic and dynamic understanding of human disease will require major additional scientific efforts as well as significant advances in bioinformatics.

The challenges involved in successful industrialization are complex, though highly underrated in the scientific community. Problems in physical design, characterization, manufacturing scale-up and quality control routinely derail or delay development programs and keep needed treatments from patients.

Critical path research

These different types of research support medical product development:

- *Basic research* is directed toward a fundamental understanding of biology and disease processes. It provides the foundation for product development.
- *Translational research* is concerned with moving basic discoveries from concept into clinical evaluation and is often product or disease specific.
- *Critical path research* is directed toward improve the medical product development process itself by establishing new evaluation tools.



FDA role

While the biomedical research community has widened its efforts to include translational research, in our report, we call for a new focus on critical path research.

Together with academia, patient groups, industry and other government agencies, we need to embark on an aggressive, collaborative research effort to create a new generation of performance standards and predictive tools that will provide better answers about the safety and effectiveness of investigational products, faster and with more certainty.

We at FDA are uniquely suited to take a major role in this effort because of our experience overseeing medical product development, assessment and manufacturing/marketing; our vast clinical and animal databases; and our close interactions with all the major players in the critical path process

This initiative is not a fundamental departure for us, but rather builds on our proven best practices for developing industry guidance and expediting the availability of promising medical technologies.

The next steps in this initiative include a series of workshops and meetings to start development of a National Critical Path Opportunities list and to identify the key priorities.

The full report and a link to provide input and comments to the National Critical Path Opportunities List is available at http://www.fda.gov/oc/initiatives/criticalpath.

Janet Woodcock, the acting deputy commissioner for operations, directed the preparation of the report.