# Congratulations FDA, 1997 Innovations Finalist

news along the pike

Center for Drug Evaluation and Research

August 1997

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*Pike's Corners . . .*



***White House Ceremony***

## Proposed Pediatric Use Rule Launched

**By Kathy Robie-Suh, M.D., Ph.D. and Rosemary Roberts, M.D.**

Under a proposed rule announced by President Clinton at a White House ceremony Aug. 13, the FDA will require new drugs and biologics to be labeled on how these medicines can be used safely in children. In addition to new drugs, the rule will also apply to many drugs already approved and being used in children. Currently, most drugs do not have adequate instructions for use in children.

In announcing the rule, President Clinton said: "The executive action that I take today simply is designed to ensure that parents and pediatricians have the information they need. Doctors have known for a long time that children respond differently than adults to many drugs. In cases—many cases—children can only tolerate vastly scaled-down doses. In some cases, their bodies simply haven't developed enough to take any dosage of a medicine that is perfectly safe for adults."

Clinton pointed out that we still don't even

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## Report from Brussels: Harmonization in High Gear

**By Roger Williams, M.D.**

Highlights from the Fourth International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 4) held last month in Brussels, Belgium, include "finalization" of 10 tripartite harmonized guidances and announcement of the next phase—the start of work on a common document that can be used in all three ICH regions. During the last seven years, ICH has worked to bring together government regulators and drug industry experts from innovator trade associations in the European Union, Japan and the United States. The ICH process results in documents that recommend ways to find consistency in the implementation and application of technical guidances and requirements for product registration so that companies can reduce or eliminate duplicate testing during the research and development of new drugs.

Following finalization of the guidances by the 12-member ICH steering committee, consisting of two regulators and two trade association representatives from each of the three regions, the regulatory bodies in each region complete the process by incorporating the guidances into their regulatory process. For

*(Continued on page 9)*

## More Understandable TV Ads of Rx Drugs on Way

**By Nancy M. Ostrove, Ph.D.**

The FDA has issued a draft guidance for industry, entitled *Consumer-Directed Broadcast Advertisements,* that clarifies how drug companies may advertise prescription drugs on television and radio without having to include detailed prescribing information.

Current rules require either that such information be included in TV and radio advertisements, or that there be a procedure associated with ads for getting product information to consumers. The guidance specifies one possible procedure for accomplishing this. On the evening the draft guidance was issued, advertisements

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***Joe's Notebook***

# Cheating on the Neurological Exam

There is nothing that makes you appreciate the importance of drug therapy in the physician's black bag more than a confrontation with your own mortality. My enforced vacation from my editorial duties for the last two issues of the *Pike* started at 10:30 a.m. June 7. (Allow me a moment to thank all the contributors and **Kevin Ropp** and **Lori Frederick** who worked long and hard to bring you the June and July issues of the *Pike*.) Returning to that Saturday morning, I had just completed my workout and gone to the refrigerator for a can of diet soda. The flip-up top was particularly tough to open and took two tries. A manufacturing anomaly, I thought. In a few moments, I was going to discover that I was the anomaly.

I sat down on the couch and noticed the can was growing heavier as I drank. Then I couldn't lift it at all. Next, I couldn't get up or move my right side. When my wife came in, I couldn't answer her. My vision was going dim in my left eye. By this time I knew what was happening—I was experiencing all the classic symptoms of a major stroke. Well, after the million dollar work-up, it turns out my symptoms weren't caused by a blood clot, a bleed, a migraine or a blood vessel spasm. I'll save the story of medical detective work for another essay. It turned out that the major arteries in my brain suffered from some kind of autoimmune inflammation that cut off blood flow enough to send parts of my brain on vacation.

There are three pieces of good news here. I haven't been left with any permanent deficits. The disease is responding to drug therapy. And, after reading **John Swann's** column on the early days of drug regulation and visiting the History Office's display on drug labeling in the Medical Library, I understand just how lucky I am to be living at the end of this century and not at its beginning.

When part of the brain is not working, the remaining parts communicate in weird ways. As my recovery in the hospital progressed, my addled brain thought it could help me hasten my discharge by rehearsing the neurological exam before the doctor came. That's the one where the doctor asks you to say your name, close your eyes and touch your nose, and tell him what month it is and who the President is. I never forgot my name. I would sit in the bed and practice swinging my hand up so that I could at least hit my forehead or chin. I didn't know what month it was, but the hospital had a calendar in the room, so, I thought, all I had to do was read. Figuring out who was President was much tougher. I needed some trigger to remind me. Then I remembered that the President is from the South.

When the doctor appeared, I'd say my name and flail away at my face. He'd ask me the month. I'd read the calendar and answer, "January!" He would have this noncommittal expression on his face. I wondered if he suspected I was cheating. Then he'd ask me the President's name. I thought "the South" and promptly and enthusiastically replied, "Jimmy Carter!"

So you can imagine my thrill at having **Kathy Robie-Suh** and **Rosemary Roberts'** story from the White House in this issue. When I was sick, I was a lot like a child, dependent in every way. So you can guess how much I appreciate President Clinton's fine concluding remarks at the ceremony.

"Children are not rugged individuals," he said. "They depend upon us to give them love and guidance, discipline and the benefit of good medical care. Today, their dependence has been justified. Their future and ours depends upon how well we continue to do this important work."

I hope you find this issue of the *Pike* reflective of the important work you do for the health of all Americans and, indeed, the citizens of the world.


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 11B-40) and its branches (Corporate Boulevard S-121, Woodmont I 200-S, and Woodmont II 3001).*







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

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***Ombudsman's Corner***

# Mediation—Ready for Prime Time

**By Jim Morrison**

All of us at CDER have, at one time or another, experienced problematic interactions, either inside the Center or with our outside contacts. These interpersonal disputes can be among the most time-consuming issues we deal with. Despite the Center's extensive efforts at improving management and supervisory practices, difficult interactions continue to surface.

I have my own theories about why we run into such problems. In this politically correct world, we have become accustomed to interacting with our coworkers, supervisors and subordinates as well as with our outside contacts through stylized relationships that are based on certain assumptions. In our communications we tend to assume that we know what other people expect and need, but we dare not ask them directly, lest we violate some ill-defined borderline between appropriate and inappropriate interactions. Instead we seek to wrap every sentence in mumble-speak so that no one knows what we are really thinking, and everyone plays the game of inferring what each of us really means. After a while, we lose sight of even our own needs and expectations.

In addition, most of us are so busy with the technical side of our work that we don't take enough time to really listen. Even when our well intentioned communications suddenly provoke unexpected responses, we too often choose to ignore them rather than engaging in a meaningful dialogue to find out what prompted the response.

Whatever the cause of a problem interaction, if you are a party to one of them, you need to know how to deal effectively with it. There are a million ways to prevent problematic interactions from occurring, but if you get into a situation in which failed communication escalates into a real problem, is there a viable solution?

Not only is there a solution, but it is becoming more available to us. The mechanism is mediation. Mediation is simply a structured, confidential conversation between two people, facilitated by a trained mediator, with the aim of coming to a mutually accepted agreement. It is widely used in communities for everything from family disputes to reducing gang violence. It is also being used increasingly as an alternative to litigation. It is highly successful, with agreements achieved in more than 90 percent of the cases.

If this seems somehow familiar, I have written about mediation before, and I have offered to mediate disputes within CDER and between our staff and outside contacts. I have not been overwhelmed with requests. However, things are changing. The FDA EEO Office has just given a one week training course in mediation to more than 20 people from all parts of the agency. The plan is to use mediation routinely as part of the EEO process for resolving complaints. I'm hoping that as mediation becomes a part of the EEO process it will spill over into other areas and become recognized as a valuable tool in resolving all types of disputes. As people use mediation, they will find it to be a safe environment in which they can turn negative or hostile feelings about their working situation into positive and productive relationships. I won't kid you; it is not always painless, and it does take some real thought and work by the parties involved. But the rewards are great, and it can be a turning point in a career stalled by misunderstandings.

> "Mediation is simply a structured, confidential conversation between two people, facilitated by a trained mediator, with the aim of coming to a mutually accepted agreement."

If you want to find out more about EEO mediation in CDER, talk with Margaret Bell (4-6645). And, as always, I'll be glad to answer your questions about mediation in general (4-5443).

*Jim Morrison is the Center's Ombudsman.*

# Reviewer Affairs Corner: Survey '97 in Hands of Number Crunchers

**By Karen Oliver**

The Reviewer Affairs Committee (RAC) wishes to thank all the primary reviewers who took the time to complete RAC Survey '97. The Survey Task Force subcommittee members enlisted the help of some local FDA experts and are entering the survey data into the computer. The results will then be analyzed, using some statistical wizardry by **Kate Meaker** and **Japobrata Choudhury. Karen Lechter** and **Harold Silver** are assisting with the coordination of all the events surrounding the survey. After the analyses are completed, results will be made available via your RAC representative.

The RAC also wishes to thank all the primary reviewers who attended the Reviewers' Day networking event in June. RAC vice-chair **Vijaya Tammara** introduced our guest speaker, **Janet Woodcock, M.D.,** who discussed some issues of interest and concern, including the FDA budget, PDUFA, full-time equivalent ceilings and parking. All members of the CDER Senior Management Team attended. The attendees enjoyed a collegial exchange of information about the RAC—its mission, purpose, bylaws, committees, special projects, accomplishments and ongoing projects. Both the nutritional food for the body as well as the intellectual food for the soul were plentiful and appealing. A special thanks to **Jean Fourcroy** and her helpmates in coordinating this yearly event.

The RAC is taking a vacation from monthly meetings in August and wishes you all a happy, hot, humid and hazy August. See you in September.

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

# Roma Egli Treks to 'Cretaceous Park '97' Adventure

**By Edward Miracco**

So you think you've taken some interesting vacations, do you? Most of us consider a week on the beach or some time with howling kids at a theme park a treat. Or maybe you've gone West and done some sightseeing in the Rockies while staying at a familiar, cushy hotel. Well, how would a paleontological prospecting trip to the Badlands of Montana suit you? Not your cup of tea, eh? It's hot, it's dry, it's dangerous, it's physically demanding. It's wonderful, according to our own **Roma Egli** of the Office of Compliance.

Roma has always been an interesting person. A been there, done that, kind of woman. But this vacation takes the cake.

Under the sponsorship of Shenandoah University in Virginia, Roma and a group of six others, including her daughter, **Carla Gorman,** a recent Shenandoah graduate, trekked to the Badlands in search of dinosaurs. What did they find? In addition to a duckbilled dinosaur and a smaller triceratops, perhaps the largest known triceratops fossil ever found! Based on initial skull measurements this one could measure a whopping 28 feet in length, potentially surpassing the previous record by a couple of feet. Additionally, tyrannosaurus teeth were found in the fossilized triceratops' skull. It is estimated that the triceratops roamed the area of Montana, known as the Hell Creek Formation, during the late Cretaceous period, about 65 million years ago. The site is about 25 miles northwest of Jordan, Mont.

While the highlight of the trip may have been the discovery of the big triceratops, excavating a smaller one was no less exciting for Roma. She and her daughter were responsible for this dig. In appreciation for her efforts, this site was given the eponymous name, Roma's Bluff. The findings of the expedition will be presented by its leader, **Professor John Happ,** at the meeting of the Society of Vertebrate Paleontology, Field Museum of Natural History, Chicago, on Oct. 9.

When discussing the trip highlights, one tends to forget how demanding this type of vacation can be. Digging for dinosaurs is no easy task, requiring surgical precision and punctilious attention to detail. It can take years of tedious chipping, picking and brushing before a complete dinosaur fossil is extricated from its surrounding rock. Since an expedition doesn't last nearly that long, a return to the site may be years off. At the conclusion of each expedition, therefore, the exposed dinosaur fossil must be protected from the elements. This is accomplished by applying an initial covering of aluminum foil followed by several layers of moist strips of plaster-impregnated burlap. None of this is made any easier by the dry heat and broiling sun of the Montana plains. Indeed, Roma admits that one of her most cherished possessions was 30 SPF sunscreen.

And let's not forget about the dangers that the indigenous flora and fauna of the region present, for example, her confrontation with a rattlesnake. She came within 5 feet of the coiled sidewinder on one of her daily return walks from a dig site. A moment earlier, the snake had struck at and missed one of her colleagues. On another occasion, she was climbing "her" bluff and accidentally grabbed a cactus plant. She has a handful of puncture wounds, each with an imbedded piece of hardened cactus spine, to prove it.

Was the exhilaration of the trip worth enduring the hardships and dangers of living away from the comforts of civilization? The answer is obvious when you hear and see Roma describe both the accomplishments and the hardships with the same excitement and animation.

She enjoyed staring down a venomous rattler almost as much as finding dinosaurs. There is always the possibility of a consulting offer from Steven Spielberg, too. But even if that doesn't materialize, the excitement, the memories, the dangers and the accomplishments have all coalesced to make this one vacation to remember.

*Ed Miracco is a consumer safety officer in the Office of Compliance.*

# FDA Warns Consumers to Avoid Dandruff Product Called 'Skin-Cap'

**By Ivy F. Kupec**

The FDA is warning consumers about treatments for dandruff or psoriasis called "Skin-Cap." These products contain prescription-strength corticosteroids, which might pose a health hazard to many people. Individuals currently using these products are advised to immediately contact their health care providers.

Abruptly ceasing use of these steroid-containing products may potentially cause a person with the more common form of plaque psoriasis to convert to pustular psoriasis, which can necessitate hospitalization and even be life-threatening. More commonly, patients may see their psoriasis worsen. This risk makes it critical for people using Skin-Cap to immediately contact their health care providers.

FDA analysis has shown that these products contain prescription levels of a potent topical steroid, clobetasol propionate. Potentially harmful side effects of clobetasol propionate, can include stretch marks, thinning skin and dilution of tiny blood vessels. Use of large amounts or long-term use of this drug also can cause more serious side effects, including hypertension, central obesity, diabetes, hairiness, acne, osteoporosis, weakening of bones, impaired wound healing, decreased resistance to infection, muscular wasting and behavioral changes such as mania and psychosis.

More importantly, it can suppress the body's ability to produce its own corticosteroids in helping it fight infection or deal with body trauma.

Skin-Cap is imported from Spain and marketed as a nonprescription spray, shampoo and cream for dandruff, seborrheic dermatitis, psoriasis and other skin disorders.

In addition to this warning, the FDA issued a nationwide

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***History Corner***

# Therapeutic DMZ Led to Rise of Federal Drug Regulation

**By John Swann**

*First of four parts*

At the turn of the 20th century, the drug supply in this country was the therapeutic equivalent of a demilitarized zone. Countless brands of worthless patent medicines swindled consumers with their egregious therapeutic claims, harmed patients with such hidden ingredients as opiates, cocaine and alcohol, and ensured their name-recognition by blackmailing newspapers into refusing to run articles critical of the nostrums. Even the so-called ethical pharmaceuticals that were employed in regular medical practices were often adulterated and of questionable potency. The drug landscape was in such a sorry state that when Congress appropriated funds in 1901 to elevate the Division of Chemistry to a Bureau, Chief Chemist Harvey Wiley announced his intention to study drugs as a second line of work. For Wiley, overwhelmingly preoccupied with foods, it was a significant step.

The American Pharmaceutical Association (APhA) had long supported increased drug control, and in 1901 it established a Committee on Drug Adulterations. It was to this association, at its 1902 annual meeting, that Wiley turned for assistance in mapping out the scope of the named but unstaffed Drug Laboratory. Wiley envisioned a drug laboratory that would help unify analytical methods to identify and standardize pharmaceuticals, and thereby instill uniformity on analytical results.

He was echoing words spoken earlier at the same meeting. The chair of the scientific section of the APhA had detailed some of the shortcomings in the methodology of drug assay of the time. Keep in mind that even though some states recognized the U.S. Pharmacopoeia as the standard compendium of drug identity, this was still before Federal recognition of the USP as an official compendium of drug standards. The chairman of the section complained that the variety of assay techniques for individual drugs had a deleterious impact on uniform analytical results. The field needed organization, he argued, some person or some institution to promote consistent methodologies for drug assays and standardization. Only two months earlier John Uri Lloyd, a prominent and influential voice in American pharmacy at the time, had nominated this chairman, Lyman Frederic Kebler, to head Wiley's drug lab.

Kebler was a likely candidate for the job. After receiving his education in pharmacy and chemistry from the University of Michigan, he moved to the Philadelphia firm of Smith Kline and French, where he became chief chemist in 1892. He published over 60 papers during his Philadelphia years, most of them devoted to drug assay and adulteration. Kebler's duties at Smith Kline and French included inspection of bulk drugs that the firm considered purchasing. This experience familiarized Kebler with drug adulteration, and by the time of the formation of the Drug Laboratory, he was a recognized expert in the field.

Science in major American pharmaceutical firms like Smith Kline and French at the turn of the century was quite different than the case 20 or 30 years later. New drug development and delivery, the hallmark of scientific research in the modern drug industry, was an uncommon enterprise in the industry until World War I. At that time, key supporting sciences such as pharmacology and medicinal chemistry were still at a nascent stage in American universities, much less American companies. Firms manifested a commitment to science in the form of drug standardization. Parke-Davis hired chemist Albert Lyons in 1880 to standardize its products, and within three years the company had introduced 20 chemically assayed fluid extracts. Other firms, including Eli Lilly and Company, G.D. Searle and H.K. Mulford, also utilized science in this way. It is also worth mentioning that a few companies, led by Mulford and Parke-Davis, made use of science of a different variety when they began marketing biological drugs such as diphtheria antitoxin in the 1890s.

Although he received his appointment to head the new Drug Laboratory in November 1902, Kebler's responsibilities at Smith Kline and French prevented him from assuming his position in the Bureau of Chemistry until the following March. Soon he would discover a problem at the very core of the bureau's technical capability, and he would learn that the Association of Official Agricultural Chemists would be an essential ally in the search to amalgamate drug analysis.

*John Swann is a historian in FDA's History Office.*

## 'Skin-Cap' Warning

*(Continued from page 4)*

import alert for detention of these products at all border entries, and the state of Florida stopped distribution of Skin-Cap from the primary distributor.

The Agency has previously expressed concern about the marketing of these unapproved products in two warning letters sent to two U.S. distributors earlier this year. Further investigation of these products recently confirmed that they also contained steroidal ingredients not identified on the product label.

Psoriasis, a chronic skin disorder that can be painful and disabling, is characterized by inflamed, red, scaly lesions, caused when affected skin cells reproduce faster than normal.

*Ivy F. Kupec is a public affairs specialist in FDA's Press Office.*

## Labeling Display Unveiled at Library

The History Office has installed a new exhibit in the Medical Library's display cases titled "Reading Between the Lines: Evolution of the Drug Label." Be sure to visit Room 11B-40 the next time you're in Parklawn.

***Reviewer's Corner***

# An ICH Reminiscence: Claire and the Mori Diagram

**By Zan Fleming**

What is the connection between my daughter Claire and the Mori diagram? Read on to find out, but first some background. The fourth round of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 4) was held several weeks ago in Brussels (see page 1). ICH has been both a reflection and a driver of the revolution in the way drug evaluators and developers communicate. One of the important things that I learned from this multicultural experience is that far more than science is involved in drafting technical documents.

I have some very fond memories of persons, places and things related to my involvement in ICH. One such memory comes from working on the guidance, *General Considerations for Clinical Trials* (E8). As with all ICH expert working groups, E8 was made up of one or more representatives from industry and the regulatory authorities in each of the three regions, the European Union, Japan and the United States. We got off to a somewhat slow start because of very different perspectives among group members about the details of how drugs are best developed. The Japanese, for example, started with a very well-ordered but linear view of the sequence in which clinical studies should be performed. This contrasted with the preference of the Western members for a more spiraling, learn-confirm approach.

"As with all ICH expert working groups, E8 was made up of one or more representatives from industry and the regulatory authorities in each of the three regions, the European Union, Japan and the United States. We got off to a somewhat slow start because of very different perspectives among group members about the details of how drugs are best developed."

Our group started to make progress when we learned that listening carefully to each other was not enough to get us through our conceptual differences. The approach that worked for us was to stop explaining ourselves and, instead, explore together relationships of basic words and concepts. In so doing, we discovered saliencies that bridged our language and behavior gaps. This did not happen immediately—time and an evolving sense of trust and affection were required before we started to pick up steam.

I could never have guessed what would bring about a turning point for our group. It came at our Washington meeting in the spring of 1996. The E8 group came to my house for dinner on the second night of our meeting. Despite having made some technical progress on paper, I was a bit anxious about whether all these individuals from different cultures would be able to have a good time together.

This is where Claire came in. First, you have to understand that Claire, at that time, was an exuberant, hyper-energetic 4-year-old. Her parents had made no effort to discourage her from firmly believing that she was a princess around whom the world revolves. She assumed, for example, that our guests were invited solely to entertain her and to be entertained by her. Almost as soon as the guests had arrived, Claire went to work. She warmed them up by presenting a stuffed animal or treasured object for each person to examine. Later, with their encouragement, she would ask for stories to be read from one of the books she carried around in a stack. The coup de grâce was delivered when she bestowed a little sticker in the likeness of a flower or cute animal to each visitor. Ceremonially, she sat on each person's lap while explaining the significance of the sticker in detail. At the end of the evening, Claire was at the door, giving each guest a loving, good-bye hug.

The next morning when I walked into the meeting room, I suddenly noticed that everyone was wearing Claire's sticker. I was touched by this gesture, but what then happened was truly astounding. One of the Japanese members, Mr. Mori of the Japanese Ministry of Health, in the year that we had been meeting, had hardly said a word until the night before when Claire was sitting on his lap. Shortly after we started, Mori-san passed out the diagram at the bottom of the next page.

Very modestly, he said, "Perhaps this might help us." Indeed it did. This diagram (see page 7, bottom) shows the imperfect relationship of the different kinds of clinical studies to the phases of drug development in which they typically occur. In expressing this deceptively simple point, the Mori diagram solved a major, but elusive goal of our group, to express the dynamic, non-linear nature of modern drug development. All the more astounding was that this epiphany came to a person steeped in the linear, set-order approach. I believe this is one of the few diagrams in the entire body of ICH documents and the only figure to depict a concept. The Mori Diagram helps to make the E8 guidance one of the more creative works to come out of ICH. Would Mori-san have felt comfortable enough to propose such a radical approach if Claire had not sat on his lap and put the sticker on his shirt? We will probably never know.

A postscript: During an E8 meeting nearly a year later in London, I was standing in a line for lunch with one of my other Japanese colleagues. He is a silent but physically imposing fellow who looks as though he might have forsaken a career as a sumo wrestler for a more restricted diet and a captaincy in industry. My colleague took out his elegant Gucci wallet and opened it. While saying only one word, he proudly revealed a worn but still discernible sticker that had been pasted on the inside cover some time ago. I am not sure exactly why, maybe I was homesick or very tired, but I had to excuse myself and find a table in the corner where a few tears would not be noticed.

*Zan Fleming is a medical officer in the Division of Metabolic*

***Information Technology Corner***

# OIT's Intranet Site to Debut in September

**By James B. Baughman**

The Office of Information Technology (OIT) Web site will be unveiled by the end of September. Over the past five months, the OIT has worked diligently to develop an intranet Web site that will encompass many aspects of computer technology. Topics not to miss when visiting the OIT Web site include:

**Support Assist:** Check out this online technical support center that includes an area on frequently asked questions (FAQ's) pertaining to hardware systems, software applications and peripheral equipment; software utility downloads; installation instructions for the popular supported CDER software applications; a sophisticated text search engine; Windows '95 and upgrade tips; and PC virus information.

**Training Schedules:** Visit this area to view training schedules for applications such as Word, Excel, PowerPoint, Access, Excalibur, Teamlinks, Calendar Manager, local area networks and the Internet. You'll find a brief description of the course and be able to download class training materials.

**Documentation:** This area contains four parts. The first, System Documentation, outlines the description, specifications and design structure of OIT developed software applications, which include the CDER Support Assist Web Site, statistical applications and others. The second part, Applications Training Documentation, includes materials such as training manuals, helpful hint FAQ sheets as well as tips and tricks on popular software applications such as MS Office, the Decision Support System, the Establishment Evaluation System, SmarTerm and others. Parts three and four encompass CDER Trifolds, handy "cheat sheets" on popular software packages, and IT MaPPs. Included is the ability to view and download these materials.

**Security:** Stop here to read about the latest in security news outside CDER. Read the latest concerning software bugs uncovered that may compromise security over the Internet, and other breaking stories. Also included will be staff manuals such as *Security of Electronic Communications Systems, Proper Use of Government ADP Resources, Off-Site Computing,* and *Policy on Use of Microcomputer Software.*

**Tip of the Day:** Don't miss the latest tips pertaining to MS Office, the Internet Explorer and Windows '95.

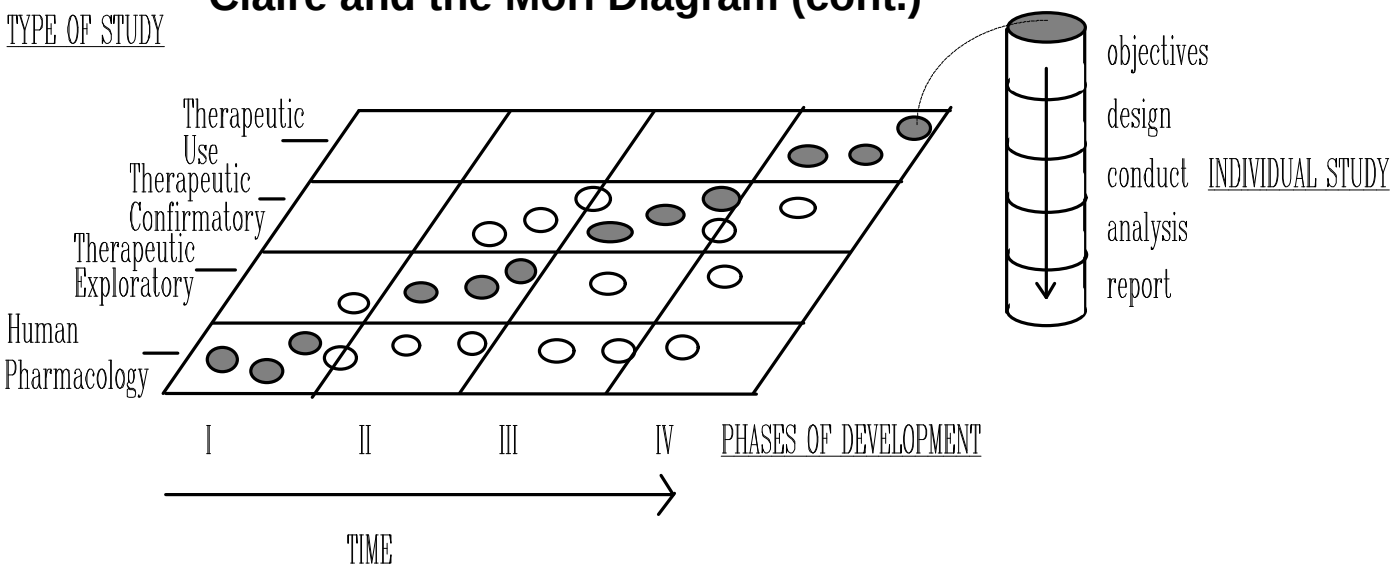
**Publications:** Keep abreast of the latest in computing technology through links to popular online computer trade magazines.

**IT Events:** Find out about the latest IT-related events on the horizon. This area provides information on commercial and FDA-sponsored IT events and technical meetings.

You'll also find an up-to-date IT focal point list and feedback forms. OIT will continually add material to the site, and all material will be kept current. OIT will announce all major new additions to the Web site via e-mail. The OIT Web Site will be best viewed with MS Internet Explorer 3.0 (or a later version) and at a monitor resolution of 1024 by 768.

*James B. Baughman is a computer specialist in OIT's Technology Services Support Staff.*

## Claire and the Mori Diagram (cont.)




The Mori Diagram illustrates the relationship between the phases of new drug development and types of study that may be conducted during each phase. The shaded circles show the types of study most usually conducted during each phase of development. The open circles show certain types of study that may be conducted during that phase but are done so less frequently. Phase I, for example, usually consists of human pharmacology studies. Each circle represents an individual study. The elements and sequence of a study are illustrated in the column that is joined to one of the circles by a dotted line.

***Project Management Corner***

# Joint FDA, DIA Project Management Training Workshop

**By Jean A. Yager**

The Project Management Coordinating Committee would like to announce a ground-breaking initiative co-sponsored with the Drug Information Association (DIA): a joint DIA/FDA training workshop in project management. The two-and-a-half day workshop, "Roles of Industry and Agency Project Management and Regulatory Staff in Drug Development and Review," is targeted for mid-level project management and regulatory staff. Seating is limited for the Oct. 29 to 31 event at the Sheraton Washington Hotel.

The program is designed to train CDER and Center for Biologics Evaluation and Research (CBER) project management and regulatory staff alongside their industry counterparts. The benefits of joint training include the pooling of faculty experts, the exchange of ideas, and the sharing of best practices used in industry and the Agency. This workshop will also provide the opportunity for FDA staff to learn from key industry experts about the drug development process and provide industry staff an opportunity to learn about FDA project management and team processes used in the review of new drug applications.

The first day of the workshop will begin with an introductory address from CDER Director, **Janet Woodcock, M.D.** Discussions of project management systems and team structures used in the pharmaceutical and biotech industries and in CDER and CBER will be followed by a panel discussion with interactive audience participation. Information regarding best practices used for team building, team motivation, project manager training and software tools will be shared via roundtable discussions.

A portion of the workshop will consist of several creative videotape vignettes that outline the processes by which an industry team and an FDA team orchestrate activities from drug discovery through postmarket approval. Each vignette will be followed by a panel discussion and ample opportunity to raise questions and present alternative approaches.

The second day will present results of a national survey on the key factors correlating to rapid development and approval of new pharmaceutical products. The last day of the session will wrap up with an interactive panel discussion of specific case studies that will demonstrate successful FDA and industry team collaboration in the development and review of new products.

The joint training workshop will be concluded with motivational closings from **Mark Elengold,** CBER's Acting Deputy Director, and **Murray Lumpkin, M.D.,** CDER's Deputy Center Director (Review Management).

The DIA has had many years experience designing and implementing successful training workshops, and we are fortunate to have the opportunity to work with them on this exciting training program. Their guidance, assistance and support has been most valuable in assuring that this training program will meet the objective of developing foundational understanding of industry/FDA processes upon which to build a collaborative approach to the development and review of new therapeutic agents.

The program co-chairs, **W. Terry Baker,** Procter and Gamble, and **Jean A. Yager,** CDER, wish to thank the dedicated FDA and industry development team.

The core FDA committee includes:

From CDER: **Linda Brophy, Linda Carter, Patricia DeSantis, Gordon Johnston, Debbie Kallgren, Dottie Pease, Matthew Tarosky** and **Mary Jane Walling.**

From CBER: **Wendy Aaronson, Suzanne Sensabaugh** and **Gail Sherman.**

The industry committee includes: **Tammy Antonucci, Ph.D.,** Amgen; **Christian Bernhardt, Ph.D.,** Procter and Gamble; **Joan T. Butler,** Otsuka America Pharmaceuticals; **David M. Cocchetto, Ph.D.,** and **Karl H. Donn, Ph.D.,** Glaxo Wellcome; **Charles Grudzinskas, Ph.D.,** G.D. Searle; **Irwin G. Martin Ph.D.,** Parke-Davis; **Donna Ohye,** Janssen; and **Biff Owens,** Chiron.

Special thanks to OTCOM's **Elaine Frost** for providing expertise in the development of the videotape vignettes for the training session. For additional information, check out the DIA's homepage at http://www.diahome.org or call DIA at (215) 628-2288.

*Jean A. Yager is the Center's Project Management Director.*

# Kathy Abel Recognized

**By Angie Youngblood**

For the past five years, I have been in charge of CDER's videoconferencing program. And while I've been called many interesting names like "VC Guru" and "Videologist," it has always been a challenge to try to be in many places at one time. That is why my office developed a training program to teach "focal points" around the Center how to operate equipment and host a videoconference.

This led to the creation of an award from the Office of Training and Communications (OTCOM) to recognize outstanding teleconferencing focal points. This award recognizes individuals who have performed above and beyond their duties by providing videoconferencing support and expertise throughout CDER. I am pleased to congratulate **Kathy Abel,** Office of Clinical Pharmacology and Biopharmaceutics, as the first recipient of the award.

Kathy is a management analyst who has been with CDER for seven years. Her continuous support and customer service has been noticed and appreciated most at Corporate Boulevard. Kathy can be found at every CDER Forum and at other CDER videoconferencing seminars. It has been a pleasure to work with Kathy on these projects. She is a quick and eager learner and a natural at videoconferencing. I look forward to our continued work together.

*Angie Youngblood is a communications specialist in OTCOM.*

# ICH 4 Finalizes 10 Guidances, Starts Common Technical Document

*(Continued from page 1)*

example, in the United States, each draft guidance is published in full in the *Federal Register*. After public comments are considered and appropriate revisions made, the final texts of the guidances are published in the *Federal Register*.

The results in Brussels mean that work on more than three-quarters of the guidances has been completed. After having made so much progress during this first phase, The ICH steering committee agreed to launch a second phase focused on maintaining the existing documents and undertaking a new topic that will create a *Common Technical Document.* This represents a logical progression from a single, harmonized set of guidances for collecting the technical data to a common technical information package for presenting the data. The goal would be to harmonize format so that the same submission could be provided to the regulatory authorities in all three regions.

ICH 4 also announced finalization of the *Medical Dictionary for Regulatory Activities* (MedDRA), which will provide a common terminology to facilitate adverse event reporting. Also, the release for consultation of the consensus draft guidance, *Specifications for New Chemical Drug Substances and Products* (Q6A), represents a step toward the goal of having the same specifications for a drug product wherever it is marketed. The draft guidance has been developed in close collaboration with the pharmacopoeial authorities in each region.

Over 1,600 people attended the conference. More than 400 of them were from regulatory agencies or other governmental bodies. The remainder primarily represented the research-based industry within the three regions. There was significant participation from industry in other parts of the world.

**Five Safety Guidances**

Although scientists are developing alternative methods of safety testing, preliminary testing in animals is still necessary to protect humans. The objectives of the ICH safety guidances include reducing unnecessary use of animals and, in the longer term, replacing them with validated alternatives that give equal or greater assurance of safety. ICH has met the first of these objectives with a series of guidances on reproductive toxicity testing and carcinogenicity testing. These have already reduced duplication and redundancy in the safety testing phase of new drug development.

The five safety guidances adopted at ICH 4 cover several areas in nonclinical testing. The guidance on *Conduct of Carcinogenicity Studies* (S1B) calls for one long-term study rather than two. A revision to *Dose Selection for Carcinogenicity Studies* (S1CR) adopts a more pragmatic approach to the recommended maximum doses used in animals. The *Standard Battery for Genotoxicity Testing* (S2B) represents scientific consensus on the most appropriate tests for predicting possible damage to human genetic material. *Safety Testing for Biotechnological Products* (S6) outlines principles for testing these specialized products for which traditional test methods may not be appropriate. *Non-Clinical Safety Studies for the Conduct of Human Clinical Trials* (M3) addresses the timing of toxicity studies in relation to the conduct of clinical trials.

Finally, the requirements for chronic testing in non-rodents have been reviewed. Previous requirements meant that, because the recommended study duration varied between 6 and 12 months, duplication of testing was necessary for the international development of new drugs. Following extensive scientific analysis, it has been possible to eliminate this duplication and agree that, for data submitted on new drugs, a single 9-month study is acceptable in all three regions. This will result in a 30-percent reduction in the number of animals used.

**Three Efficacy Guidances**

The efficacy guidances address important aspects of clinical study design, conduct, reporting and interpretation. They also provide the expectations of regulatory authorities for the kinds of studies indicated in a global drug development program. After their final drafts were signed-off in Brussels, three efficacy guidances joined over a half dozen other completed efficacy documents. *General Considerations for Clinical Trials* (E8) sets out the basic principles of clinical drug development and the design and conduct of clinical studies. *Statistical Considerations in the Design of Clinical Trials* (E9) provides a succinct but comprehensive discussion of biostatistical terms, concepts and preferred approaches. Since E8 and E9 deal with concepts pertinent to both the drug developer and the drug evaluator, they have value as Good Review Practice (GRP) references. *Clinical Safety Data Monitoring: Data Elements for Transmission of Adverse Drug Reaction Reports* (E2B) provides terminology and appropriate mechanisms for reporting safety information during the investigational phase of drug development.

**Two Quality Guidances**

ICH has already reached agreement on eight guidances related to the quality of products containing new chemical drug substances and an additional four related to biotechnological products. Agreement at Brussels on the *Derivation and Characterization of Cell Substrates* (Q5D) completes the set of biotechnological guidances and provides additional assurance of product consistency and safety. The guidance on *Residual Solvent Impurities* (Q3C) is a result of an extensive analysis of data on the safety of solvents used in drug manufacture.

The CDER coordinating committees and technical working groups have made tremendous contributions to the ICH effort. Also representing CDER at Brussels were: **Doris Bates, Bill Calvert, Yuan Yuan Chiu, Peter Cooney, Joe DeGeorge, Zan Fleming, Ken Furnkranz, John Gibbs, Jaime Henriquez, Chuck Hoiberg, James MacGregor, Justina Molzon, Bob O'Neill, Bob Osterberg, Rashmikant Patel, Eric Sheinin** and **Bob Temple.**

The guidances will soon be on CDER's Web site, http://www.fda.gov/cder/guidance/index.htm. They are now on the ICH Web site, http://www.ifpma.org/ich1.html.

*Roger Williams, M.D., is the Deputy Center Director (Pharmaceutical Science) and is FDA's lead delegate to the ICH steering committee. As Deputy Center Director, he is responsible for CDER's international activities.*

# Proposed Rule Requires Pediatric Data Before Drug Approval

*(Continued from page 1)*

have good information about medication for some of the most common childhood illnesses. And we certainly don't know enough about medications for treating many life-threatening diseases in children. Clinton added that less than half the drugs used to help the estimated 12,000 children with HIV infection in our country have been tested for use in children. Information is especially sparse for children under two, the time when the medication may be most needed.

"Without clear guidance, pediatricians sometimes decide not to prescribe for children drugs used successfully by adults," Clinton said. "This means that the children may well be deprived of what may be the very best treatment available. And as the Vice President said, the pediatrician's other alternative is to guess—with potentially grave consequences. Some time ago, for example, doctors gave infants small doses of a crucial antibiotic commonly used by adults, but it turned out that the infants were unable to clear the drug from their bodies and large amounts built up in their livers and, because of needed dosage studies that had not been done, 23 infants died."

The proposed rule is designed to end this guessing game. It ensures that new drugs and biological products that are likely to be commonly used, or that show promise for use in children, contain adequate pediatric labeling at the time of, or soon after, initial approval. For drugs that are already marketed, the rule would codify FDA's authority to require, in compelling circumstances, that manufacturers conduct studies to support pediatric-use labeling.

In 1994, the FDA issued a regulation that simplified the pediatric data requirement to encourage drug manufacturers to submit these data voluntarily for review. However, many new drugs are still being developed without information on how they should be used in children.

"Kids deserve the same knowledgeable access to newly developed drugs that their parents get," said Donna E. Shalala, Secretary of Health and Human Services. "With this proposal, we will have the power to ensure pediatricians and other health care providers who treat children have the best scientific information available on which to base their medical decisions."

The proposed rule would allow post-approval submission of pediatric data if the FDA had concerns about testing the drug on children prior to approval.

Likewise, the requirement could be waived if the FDA found that:

- The product was likely to be unsafe or ineffective in pediatric patients.
- Pediatric studies were impossible or highly impractical.
- Reasonable efforts to develop a pediatric formulation had failed.

Under the proposal, when a company initially seeks permission to test an experimental drug, CDER officials would decide if it has potential for children. If it does, the company would be required to prepare a plan for developing the appropriate pediatric data. In many cases, the testing would not require clinical efficacy trials. A drug previously found safe and effective for adults would undergo testing to determine the safe dose in children if the disease was the same in children and adults.

The comment period on the proposed rule will last for 90 days. Comments will be reviewed and considered by the agency in developing the final rule. The proposal can be found on CDER's Web site, http://www.fda.gov/cder/guidance/index.htm.

"When something like this happens, the President gets to give a speech," Clinton remarked, "but the credit goes to all the people who worked on it—to all the parents, to those who kept working for this even after their children suffered terrible injury and sometimes even death; to all the members of the professional groups. You deserve the credit. And I am very grateful to you for bringing this matter to my attention and giving me the power to use what the law has given me as President to do what you know and to do what you have long known is the right thing to do. This is your day."

Well-deserved credit goes to a number of people within FDA. The proposed rule is the result of months of work initiated by the Office of the Commissioner to focus on getting more drugs labeled for use in children. **Ann Witt** in the Office of Policy, Office of the Commissioner, coordinated the drafting of the proposed rule. The draft was reviewed by the CDER Pediatric Subcommittee as well as by offices in CDER and CBER. Members of the Pediatric Subcommittee and others involved in developing the rule were invited to the White House Ceremony.

*Kathy Robie-Suh is a medical officer in the Division of Gastro-Intestinal and Coagulation Drug Products and a member of the Pediatric Subcommittee. Rosemary Roberts is a group leader in the Division of Anti-Infective Drug Products and chair of the*

***EEO Corner***

# 2 Minority Interns Contribute

**By Noreen Gomez**

This is the second year that CDER's EEO Office participated in the Minority Health Professional Foundation Fellowship program and financed two summer interns. This year, **Angela Riley** from the College of Pharmacy and Health Sciences, Texas Southern University, and **Joynell Sparrow** from Xavier University of Louisiana spent nine weeks in CDER.

For the first half of her internship, Riley, a fifth-year pharmacy student, helped complete a complex labeling guidance for generic versions of naproxen. The document will serve as the labeling model for all generic naproxen products. Riley also helped review many labeling supplements for Office of Generic Drugs (OGD). The last half of her internship was spent learning how OGD establishes bioequivalence for drug products.

Riley received her supervision from **Charlie Hoppes, Jerry Phillips** and **Peter Rickman** in the Division of Labeling and

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# CDER Paves Way for More Understandable TV Ads of Rx Drugs

*(Continued from page 1)*

conforming to its specifications began appearing on network and cable television.

Prior to issuance of this draft guidance, drug companies that wanted to advertise prescription drugs in broadcast media either produced ads that discussed the disease or condition treated by a product but didn't mention the drug name; or they produced ads that mentioned the product but didn't say what it was used for. Neither of these kinds of ads require detailed product risk information. However, these ads are generally vague and result in a great deal of consumer confusion. By indicating how drug companies can ensure that consumers have convenient access to detailed product risk information, the new guidance should encourage ads that provide more specific information and promote consumer awareness of prescription drugs and their uses.

Under the law, any advertisement for a prescription drug must contain a "brief summary" of all important information about the advertised drug, including its side effects, contraindications and effectiveness. The advertising regulations further specify that advertisements broadcast over radio, television or through telephone communications systems must include a "major statement" that prominently discloses the most important risks associated with the drug. The regulations also state that the statutory "brief summary" requirement for broadcast ads can be met by ensuring "adequate provision" for disseminating the advertised product's approved package labeling.

In practice, print advertisements for prescription drugs generally meet the "brief summary" requirement by printing the risk-related sections of drug labeling together with the advertisement. Providing that amount of information in TV and radio advertising is far more difficult because of time and space constraints.

Because the Center had never specified how, exactly, sponsors could achieve "adequate provision" for consumer-directed broadcast advertisements, sponsors believed that they needed to present a brief summary in product claim advertising, which essentially precluded TV and radio advertising. The draft guidance remedies this situation by describing one possible mechanism for fulfilling the "adequate provision" requirement. This approach presumes, however, that the broadcast ad is truthful, not misleading and presents the most important risks associated with the drug.

To fulfill the "adequate provision" requirement, the advertiser should provide a mechanism to ensure that the diverse population of consumers exposed to the ad can easily obtain the full product labeling. One acceptable mechanism is outlined in the draft guidance and includes all of the following four components:

- Reference to a toll-free telephone number for consumers to access detailed product information in a timely fashion—sent by mail or fax, or read to them over the phone.
- Reference to direct-to-consumer print ads appearing concurrently in publications that reach the target audience. Reference to brochures containing similar information would also be acceptable if the brochures were made available in a variety of easily accessible sites such as doctors' offices, libraries and stores.
- Reference to an Internet Web page address with full access to the approved product labeling.
- A statement that pharmacists, physicians or veterinarians (in the case of animal drugs) can provide additional information about the product.

In addition to supplying the required information, broadcast advertisers are being encouraged to provide consumers with non-promotional, consumer-friendly information about their advertised products.

The Division of Drug Marketing, Advertising and Communications (DDMAC) will collect information on the broadcast advertising that occurs as a result of the draft guidance. DDMAC is also urging broadcast advertisers and others to collect data on the effects of broadcast advertising, and consumer-directed advertising in general, and to provide it to the Center. CDER will evaluate the effects of this guidance within the next two years to determine whether refinements are needed.

The draft guidance represents the first step of an intensive Agency review of concerns about the value of requiring extensive detailing of product risk information in consumer-directed prescription drug advertising.

Many individuals contributed to the issuance of this guidance, including members of the Intra-Agency Working Group on Promotion and Advertising, DDMAC staff, the Center Director's Office and the Agency's Office of Policy.

*Nancy M. Ostrove is a public health analyst in the Division of Drug Marketing, Advertising and Communications and the Agency's expert on consumer-directed advertising.*

## ***EEO Corner***

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Program Support, and **Nick Fleischer** and **Nhan Tran** in the Division of Bioequivalence.

Sparrow, a prepharmacy sophomore, worked in Division of Reproductive and Urologic Drug Products on a labeling project and learned basic pharmacokinetic and pharmacodynamic principles on a project with the clinical pharmacology and biopharmaceutics review team supporting the division.

She also learned library research skills using Medline, gained experience with computer software packages, was exposed to the clinical pharmacology and biopharmaceutics regulations used to review new drug applications, and gathered background information to begin the review of a relative bioavailability study.

Sparrow received her supervision from **Angelica Dorantes, Sam Haidar, Venkateswar Jaarugula, Heidi Jolson** and **Lana Pauls.**

*Noreen Gomez is a member of the Center's EEO Staff.*


# FDA Jumps Hurdle in Innovations Competition

The FDA has been named one of 25 finalists in the Innovations in American Government Awards Program sponsored by the Ford Foundation and Harvard University's John F. Kennedy School of Government. The agency was recognized for innovations in the U.S. drug approval process. May's *Pike* covered the Agency's selection as one of 99 semifinalists from competition among 1,500 applications.

"This honor is especially exciting for CDER because this award is for innovations in the new drug review process," said **Murray Lumpkin, M.D.,** Deputy Center Director (Review Management). "It recognizes the PDUFA program, including different performance goals for prioritized applications, and the expanded access programs for serious and life-threatening illnesses."

The Innovations Awards Program recognizes governmental initiatives that provide creative solutions to pressing social and economic problems.

# ODE IV Reorganization Highlights Cross-Divisional Teams

**By Toni Nearing**

The Office of Drug Evaluation IV, directed by **David W. Feigal, Jr, M.D., MPH,** is in the midst of a reorganization. The Office was once composed of two of the largest-staffed divisions within CDER, the Division of Anti-Infective Drug Products (approximately 61 employees) and the Division of Anti-Viral Drug Products (approximately 82 employees). It has now launched a third division—the Division of Special Pathogens and Immunologic Drug Products.

The evolving ODE IV community is also focusing on structural and functional improvements to the current review processes. In planning for this reorganization, ODE IV staff spent much time and effort identifying and evaluating the procedural differences between the two parent divisions. What has worked well? What has not worked well? Do these processes make sense? Do the two divisions do things the same way? If not, what are the differences? Are these differences important?

Equally important to this internal evaluation was industry's perception of how ODE IV does business. Traditionally within CDER, the Pharmaceutical Research and Manufacturers Association (PhRMA) schedules a two-hour dialogue session with a review division as a way of exchanging information. When PhRMA approached Dr. Feigal about having such a session with the Division of Anti-Infective Drug Products, they agreed that, because of the pending reorganization, a longer dialogue session with representatives from all three divisions would be optimal. Volunteers from ODE IV and PhRMA formed five working groups based on the phases of drug development and collaborated for three months, from March through May 1997, identifying areas for improvement and strategies to consider.

It was not coincidental that the essence of these five ODE IV and PhRMA working groups was captured in the currently proposed cross-divisional team structure of the ODE IV reorganization. These cross-divisional areas include:

- Pre-IND.
- Biopharmaceutics and clinical pharmacology.
- Postmarketing safety, promotion and labeling.
- Computer and information sciences.
- Laboratory Research.

These cross-divisional teams are designed to provide consistent, efficient and quality review support to the three divisions in ODE IV using existing divisional resources in well-defined areas of the drug review process. Current plans are for these cross-divisional teams to receive oversight from the Office Deputy Director.

The ODE IV community is currently working on defining the responsibilities of these teams. As information becomes available, we will post it on the ODE IV intranet home page, http://ode4serv.cder.fda.gov.

*Toni Nearing is special assistant to the ODE IV director.*

## Pregnancy Labeling Hearing

**By Rose E. Cunningham**

A public hearing on pregnancy labeling categories will be held Sept. 12 from 9 a.m. to 5 p.m. at the Holiday Inn Bethesda, 8120 Wisconsin Avenue, Versailles I and II. This public meeting will elicit comments on the practical utility, effects and limitations of the current pregnancy labeling categories. The meeting will help CDER officials identify the range of problems associated with the categories, identify and evaluate options that might address identified problems, and hear views of the groups most affected.

The hearing will focus on the requirement that each drug product be classified in one of five pregnancy categories intended to aid clinicians and patients with decisions about drug therapy. Public comments and FDA's preliminary review of the pregnancy category designations for marketed drugs suggest that the categories may be misleading and confusing, may not accurately reflect reproductive and developmental risk, and may be used inappropriately by clinicians in making decisions about drug therapy in pregnant women and women of childbearing potential and also in making decisions about how to respond to inadvertent fetal exposure.

Written notices of participation and comments for consideration at the hearing must be submitted by Aug. 28. For further information, contact me at 301-594-6779 or follow the Internet link to the *Federal Register* notice for mailing and shipping instructions of required information.

*Rose Cunningham is a regulatory health projects manager in the Center's Executive Operations Staff.*