news along the pike

AUGUST 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

VOLUME 6, ISSUE 8

INSIDE . . .

PIKE'S CORNERS

ICH Common Technical Document Released

FDA Hopes to Gather Comments in Time for Nov. Meeting

BY NORMAN J. OLIVER

FDA officials announced on Aug. 24 that they are seeking comments by Sept. 30 on the draft guidance for the common technical document, developed under the auspices of the International Conference on Harmonization. The short comment period will allow FDA time to review comments before the November biannual ICH meeting in San Diego. That forum will be the first in which the document is publicly discussed. The draft is formally titled *M-4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use*.

Comments to portions of the guidance made available in February were used in developing the current draft. This version was officially released by the ICH steering committee at its July meeting in Brussels, Belgium. Copies are posted on the Center's Internet site at http://www.fda.gov/cder/guidance/index.htm.

The draft—detailed and more than 200 pages in four parts—provides highly specific outlines and example data tables for new drug applications. Manufacturers following a final M-4 guidance will be able to submit the same content in the same format to the regulatory

(Continued on page 12)

Weather, Flight Delays Challenge FDA Officials on Trip to ICH

BY JUSTINA MOLZON, M.S., PHARM, J.D.

BRUSSELS, Belgium—FDA officials spent up to three days travelling from Rockville to meetings here for the International Conference for Harmonization steering committee and its technical expert working groups from July 17 to 20. Travel schedules were disrupted by bad weather and a work slowdown on a major U.S. airline.

The steering committee agreed to release the common technical document for comments in the United States, Japan and the European Union. Following consideration of the comments, they expect to release a final version in San Diego in November at the time of the ICH 5 meeting

The expert working group on electronic standards for transfer of regulatory information expects to have an electronic version of the common technical document to be ready six months after the completion of the entire project.

The steering committee reached Step 4 agreement on two guidances, which will now be implemented: *Choice of Control Group in Clin-*

(Continued on page 12)

Dr. Woodcock's State of Center Address Planned for Sept. 6

BY KAREN ZAWALICK

The Committee for Advanced Scientific Education once again kicks off the academic year with the State of the Center address and a rousing game of Jeopardy.

Center Director **Janet Woodcock, M.D.,** will present her address during the Scientific Seminar on September 6 from 2 p.m. to 3:30 p.m. in the auditorium at the University of Maryland Shady Grove campus. Light refreshments will be served beginning at 1:30.

Back by popular demand, "CDER Jeopardy" will inaugurate Scientific Rounds on Sept. 13 from 1:30 p.m. to 3:00 p.m. in Parklawn Conference Rooms D and E. Office directors and review staff will once again match wits answering questions based on regulatory decisions and guidelines with a sprinkle of CDER factoids. Due to its interactive nature, this event will not be videoconferenced.

Seminars and Rounds will take place on alternate Wednesdays in Parklawn with videoconferencing to Woodmont II and Corporate Boulevard. A complete listing of this fall's CDER Seminars and Rounds is available on CDERnet under the Division of Training and Development's homepage at http://cdernet/dtd/index.htm.

Karen Zawalick is an educational specialist in DTD and CASE executive secretary.

JOE'S NOTEBOOK

Missing Premises: Tool or Trap?

> I myself began to think that it [blood] had a motion, as it were, in a circle, which afterwards I discovered to be true.
>
> —William Harvey, M.D.
> *Exercitatio Anatomica De Motu Cordis et Sanguinis in Animalibus,* 1628

Scientists often accuse journalists like myself of sloppy thinking—jumping to conclusions, arguing from analogy or short-circuiting our arguments by not stating our assumptions or premises. I was looking for a good example of arguing from an unstated premise that might illustrate my article on page 4. Who better to turn to than William Harvey, M.D., (1578-1657)? The discoverer of the circulation of the blood, he is the founder of modern physiology and often credited with bringing quantitative methods to biomedical research

Displaying the Renaissance infatuation with symmetrical design, Harvey places his great insight about the circulation of the blood as a hypothetical, personal and almost introspective thought at the pivotal point of his classic treatise. Previously, he had demonstrated the action of the heart and showed the continuous flow of blood in one direction from the veins to the right side of the heart, then through the lungs to the left side of the heart, and finally to the arteries. From this point forward, he goes on to provide the evidence and supporting observations that will prove his discovery.

His brief work, a classic of early modern science and still widely read today, is a model not only for the presentation of scientific evidence but also for persuasive argumentation. Harvey often turned to metaphor, vivid description and pointed example to buttress his argument. At the pivotal point, however, he uses a classic technique designed to recreate for his readers his own epiphany. The device is the rhetorical syllogism, technically called an *enthymeme.* A frequent example of a logical syllogism is:

- All men are mortal.
- Socrates is a man.
- Therefore, Socrates is mortal.

The rhetorical syllogism omits one of the premises in the expectation that the audience will supply it for themselves and then experience their own *eureka!* moment. Harvey's unstated premise, an axiom of premodern physics, is that perpetual motion is circular. Here is how he might have stated his hypothesis in a logical syllogism:

- All perpetual motion is circular.
- Blood moves continuously in one direction.
- Therefore, blood moves in a circle.

Now that you know what you're looking for, you can read Harvey's treatise on-line at http://www.fordham.edu/halsall/mod/1628harvey-blood.html and recreate the moment of epiphany for yourself.

Correction: Once again, I find myself tripped up by an unstated assumption—that CDER employees are friendly and cooperative. "I would like to correct the statement—that 'Americans are not as friendly as they first seem,'" **Stefanie Schulte-Loebbert** writes about the story quoting her in last month's *Pike.* "We were talking about going out to clubs and bars. I realized it is easy to meet new people but I also noticed that everything is superficial. I wasn't speaking about my colleagues at work, and I don't want them to think that I think they are unfriendly. It's the opposite! They are so kind, and whenever there is a problem I can ask them and they try to fix it. I really like all of them!"

news along the pike

The Pike is published electronically on the X:drive in Cdernews and on the World Wide Web at:
http://www.fda.gov/cder/pike.htm
Photocopies are available in the Medical Library (Parklawn Room 11B-40) and its branches (Corporate Boulevard Room S-121 and Woodmont II Room 3001).
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Have ideas, news or comments to contribute?
Please contact a member of the Editorial Board or:

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OMBUDSMAN'S CORNER

Pride and Prejudice

BY JIM MORRISON

Political comedian Mort Sahl said of President Eisenhower that once he had made his mind up, he was thoroughly confused. Historians have made similar comments about George Washington's alleged indecisiveness. These were meant as criticisms, but I sometimes wonder. Are the pundits and historians identifying true indecision or are they mistaking a willingness to revisit decisions for weakness or indecision? Being always willing to review a decision and to change it in light of new information is a rare virtue. Sadly, it is rare because of the tendency in most of us to exhibit pride and prejudice.

We take pride in making the right decision. Pride in itself is fine. All of us should take pride in our work and in our lives. But pride sends us astray when it prejudices us so that we are reluctant to revisit a decision in the light of new information or a reanalysis of old information.

Almost every significant decision in life must be made with less data than one would like. This is certainly true of governmental decisions, whether made by the president or by regulatory staff at the FDA. We should recognize that such decisions are inherently susceptible to challenge later. However, having pride coupled with prejudice about a decision leads to a reluctance to reexamine it when new data become available. And that unwillingness may lead to flawed decisions subsequently. Such reluctance can also create a delay in acting on new information.

Specifically, if the new information were adverse to a newly approved drug, the consequences to the public of a delay in action caused by a reluctance to reexamine the decision could be grave. On the other hand, this pride and prejudice can lead to an unwillingness to accept supervisors' and managers' reviewing a decision and overruling it. It can also bias a reviewer whose negative recommendation regarding a drug's effectiveness was overruled, causing him or her to unnecessarily restrict labeling or to suggest new studies in a supplemental application that would not otherwise be needed.

Fortunately, decisions made in CDER are generally institutional rather than individual, so it is unlikely that one person's pride and prejudice will have a major effect. The true danger of such bias is when a group of individuals adopts a bias about a collective decision.

The institutional nature of our decisions should be a basis for curbing our pride and prejudices. None of us is fully responsible for Agency decisions, whether we think they are good or bad. That should allow us to distance ourselves from our decisions and to be willing to revisit them when new data or analyses come to light.

Jim Morrison is the Center's ombudsman.

Practice of 'Leaving' Votes with Advisory Committee Chairpersons Halted

The Center has issued an interim policy clarifying voting procedures at advisory council meetings and banning the practice of some members "leaving" their votes with the committee chairperson when departing early, usually to catch flights.

The announcement, made by Deputy Center Director (Review Management) Murray Lumpkin, M.D., in a July e-mail to Center employees, is designed to prevent confusion about and inconsistency in the voting procedures during CDER's advisory committee meetings.

"This is being issued now because we have had some confusing moments recently with some advisory committees during which members left early and left their votes with the chair," Dr. Lumpkin wrote.

"In essence they were voting when not present at the meeting and, in some cases, without having heard some (or even much) of the discussion. People, inside and out of CDER, have raised with many of us their feeling of discomfort with this procedure. As such voting practice is inconsistent with our regulations on advisory committee voting, it is imperative that we have a clear policy on this matter and that this policy is implemented consistently."

Interim policy on advisory committee voting:

- Defines "being present."
- Bans absentee votes.
- Bans official vote when quorum is lacking.
- Permits individual poling of remaining members.

In addition to banning the practice of leaving votes with the chair, the interim policy makes these specific points:

- *Defines "being present."* In order to vote on an issue before an advisory committee, a member must be present at the time the committee as a whole votes on the matter. Being present means either being physically present in the meeting room or on a telephone or videoconference link if that is the means by which the member is attending the meeting.
- *Bans absentee ballots.* A member who leaves a meeting before a vote may not vote on any issues that come before the committee after he or she leaves the meeting. Specifically, a member may not leave the meeting and "leave" their vote with the chair.
- *Bans official vote when quorum is lacking.* If members leave a meeting before the meeting's conclusion and a quorum of the committee is no longer present, the committee chair will announce this. Absent a quorum, there can be no "official" vote of the committee, and the committee chairperson will also make this announcement.
- *Permits individual poling of remaining members.* In the absence of a quorum, individual members can still be asked to express their individual opinions on the issues before the committee; however, no official vote may be taken.

The policy will keep the Center's procedures consistent with federal regulations governing advisory committee meetings. The policy will be made formal following good guidance practices.

COMMUNICATIONS CORNER

'Frame Shifting' on Biomedical Issues Can Trip Scientist

BY JOE OLIVER

People have conventional ways of dealing with issues and view them through "frames" specialized for the forum in which the issue is presented.

Below, I show three of the most common frames and forums dealing with biomedical issues with their associated behaviors, strengths and weaknesses. Problems and opportunities occur when an issue shifts from one forum to another or when it is viewed through a frame inappropriate for the forum. The shift may occur suddenly and may be intentional or inadvertent.

I developed the chart below when I was taking a graduate course in rhetoric and simultaneously involved in the public affairs aspects of the NIH's clinical trials on carotid endarterectomy, the surgical procedure to remove blockages in one of the large neck arteries supplying blood to the brain.

The debate about the surgery was confrontational and hammered hard on the physician-surgeon fault line that runs through medicine. It had slipped from the confines of doctors, offices and the pages of medical and scientific journals onto the pages of the popular media. People trained in academic discussion suddenly found their comments and opinions used in policy debate, and professional collegiality was a notable casualty.

We have one set of methods and behaviors that we use in scientific discussions. Our objective in these is truth. But we often have to make decisions without all the data we would like, and we're stuck dealing with opinions as much as fact. For medical and personal problems, we consult with family, friends and experts to uncover the best opinions and arrive at a probably true course of action. We often deal with public issues as choices among fixed alternatives, each with its own set of supporters and advocates.

I hope you find the chart useful the next time you think you're involved in a scientific discussion and the other party is behaving as though the discussion is about public policy choices.

	Scientific Method	Patient-Physician Consultation	Public Policy Discussion
Objective	New knowledge leading to the next experiment	Individual or group decision about a private contingent matter	Community action about a public contingent matter
Method of inquiry	Formal deduction from proven principles or statistical inference from an appropriately sized sample	Probable reasoning: deduction from commonly accepted premises or induction based on best applications and practices	Probable reasoning: "deduction" from commonly accepted but unstated premises or "induction" from one or a few examples
Transparency of method	Highly transparent	Somewhat transparent	Opaque
Audience	Community of similarly trained scientists	Group itself or the one member seeking advice	Public or those required to implement a program
Relevance of speaker's character	Not relevant	Somewhat relevant	Highly relevant
Basis of authority	Truth revealed through scientific method doesn't require additional support	Personal experience or expertise in a particular discipline or methodology	Personal power and charisma or power derived from an institutional position
Values emphasized	Impartiality, scientific method, quality of research, elegance of proof	Collegiality, mutual support, team building	Aggressiveness, collaboration, alliance building
Relevance emotions and intuitions	None	Somewhat relevant	Highly relevant
Propriety of questioning motives	Inappropriate. Ideally, scientists motivated by quest for truth	Somewhat open to challenge	OK to probe private and public associations, but may go unchallenged
Time frame	Permanent, natural laws	Present, immediate future	Long-term future
Communication structure	Formal	Informal	Formal
Strength with which claim is accepted	Very high among scientists or when the science is widely understood or accepted. Less high for science's public policy claims	High so long as group remains cohesive & its values go unchallenged	Very high because it relies on widely accepted but unstated premises that aren't specifically addressed for truth or relevance
Associated professions	Scientists, engineers	Health care providers	Lawyers, journalists

Schwetz, MacGregor: Partnership Key to Improved Safety Assessment

BY CLAUDIA R. TURNER

GROTON, Conn.—**Bernard Schwetz, DVM,** Acting Deputy Commissioner of FDA, and **James MacGregor, Ph.D., DABT,** Director of the Office of Testing and Research, were featured speakers at a special drug safety symposium held to mark the Aug. 21 ground-breaking ceremony for Pfizer Inc.'s new 132,000 square-foot Drug Safety Technology Center.

Dr. MacGregor's presentation, "Evolution, Revolution and Emerging Strategies in Preclinical Safety Evaluation," emphasized the opportunities for improved approaches to safety assessment created by recent advances in our understanding of molecular defense systems and the revolution in molecular and genomic technologies. He noted that collaborative approaches to bringing new scientific advances into the drug development process offer many benefits to consumers, FDA, and the industry.

Dr. MacGregor is currently on a special detail to Center Director **Janet Woodcock, M.D.,** to examine the CDER's approaches to partnering and collaboration in order to better "leverage" CDER's research resources.

The current biological markers of cell integrity, homeostasis, and morphologic damage have been defined and used for about 50 years. Dr. MacGregor believes that scientific advances have created a major opportunity to introduce better markers of cell integrity and tissue damage that can be used in nonclinical studies and confirmed in clinical trials through the use of noninvasive imaging.

He predicts that new "humanized" transgenic models, improved methods of human cell culture, and imaging of molecular perturbations will allow major improvements in our current nonclinical and clinical approaches to safety evaluation.

In the current era of rapid scientific progress, a major concern for industry has been whether FDA will accept data from new technical methods. Dr. MacGregor said the current guidance system allows flexibility and that new methods will be accepted when scientific consensus is achieved in the scientific community and within CDER. This requires understanding the relationship of new biomarkers to health; how well data derived from new methods compare to that from established methods; and the reproducibility, accuracy, sensitivity and robustness of new methods

To achieve this level of consensus, Dr. MacGregor cited the need for close collaboration between FDA, industry, and public and private institutions. He cited examples of current CDER collaborative initiatives, including the Product Quality Research Institute and the Nonclinical Studies Subcommittee of the Advisory Committee for Pharmaceutical Science.

He expressed optimism that such collaborations will lead to improved pharmaceutical development and regulation, and that this will translate into more selective drugs, improved therapeutic monitoring, and the ability to tailor dosage to individual genotypes.

Dr. Schwetz spoke about "FDA Science: Product Safety Issues." He noted that Pfizer's Drug Safety Technology Center is important to FDA as well as industry and discussed various issues that we face collectively. He indicated that, in science, it's increasingly difficult to keep abreast of the glut of new information. To address this problem, we must capitalize on the convergence of information technology and science.

We also need more predictive models in preclinical testing, better biological monitoring, and more extensive application of high throughput technology--including microarray technology such as that used in gene chips.

Dr. Schwetz feels strongly that toxicologists must be full participants in the genomics explosion and its associated ethical and testing issues. Mechanism-based toxicology testing is one area in which Dr. Schwetz said he thought marked progress had been made.

The Agency and industry are also encountering connectivity issues, he said. Both are guilty of doing too little to gain public understanding and trust. This has been especially pronounced in terms of drug availability and diversity—not only in the work force, but also in clinical trials. Dr. Schwetz pointed out that the Internet has made society much better informed, and both FDA and industry must do a better job of answering their questions.

Claudia R. Turner is a writer for the Pfizer Drug Safety Technology Center.

Pike's Puzzler: Check Your OTC Smarts

BY TONY CHITE

1. Drugs may be deemed unsafe for nonprescription or over-the-counter sale if they:

a. Are for medical conditions that can't be readily diagnosed.

b. Are habit-forming or toxic.

c. Have too great a potential for harmful effects.

d. B and C only. e. All of above.

2. Which of the following statements about liquid measurement is false:

a. 1 tablespoon equals 3 teaspoons.

b. 1 cc (cubic centimeter) equals 1 mL (milliliter).

c. 1 teaspoon is approximately 10 mL.

d. 1 liter is 1,000 mL.

3. He was born July 26, 1875, in Kesswil, Switzerland. His four functions of the mind—thinking, feeling, sensation and intuition—form the theoretical basis for the Myers-Briggs Type Indicator. His name is:

a. Eric From. b. Sigmund Freud. c. Ivan Pavlov. d. Carl Jung.

4. His remarkable accomplishment of hitting safely in 56 consecutive Major League Baseball games has so far been an insurmountable record. His name is:

a. Cal Ripken Jr. b. Joe DiMaggio c. Lou Gehrig d. Mark McGwire

5. The actress who played Theodore "Beaver" Cleaver's mother in the 1960's TV series *Leave it to Beaver* was:

a. Barbara Billingsley b. Donna Reed c. Shirley Booth d. June Lockhart

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

Tony Chite is a CSO in the Center's Freedom of Information Division.

TRAINING AND DEVELOPMENT CORNER

Molecular Genetics Lectures Now Available in Article Format

BY SAKTI P. MUKHERJEE, M.D., D.SC.

Five lectures from the series on Advanced Topics in Molecular Genetics presented last fall have been converted to article format and placed on the Division of Training and Development's CDERnet site.

Advances in mapping and decoding human genes have offered clearer insight into the basic molecular structures underlying not only physical development and attributes but also susceptibility to diseases and tolerance to drugs.

CDER's Committee for Advanced Scientific Education sponsored a popular series of lectures on this emerging technology that has opened a new era in drug development. The lectures, presented by eminent research leaders at several leading national laboratories and from the pharmaceutical industry, were received with great interest by CDER reviewers.

Some of the lectures were recorded on audio tape, and DTD's Science Education Team has converted them into articles. They incorporate the slides used by the speakers within the text to create the sense of revisiting the original lectures and provide a learning resource for CDER reviewers.

The lectures covered DNA and RNA biotechnology and its application in drug discovery, drug development and preclinical toxicology. The speakers also discussed some major ethical issues. The series, edited by **Sakti P. Mukherjee, M.D., D.Sc.,** and prefaced by **Robin Huff, Ph.D.,** 1999-2000 CASE chair, contains the following articles:

- "Genomics: From genes to drugs," by William A. Haseltine, Ph.D., Human Genome Sciences Inc.
- "Use of mRNA technologies in NCI drug discovery," by Robert Strausberg, Ph.D., National Cancer Institute.
- "Safety toxicology: An industry perspective," by Jeff Mooney and Sophie Wildsmith, SmithKline Beecham Pharmaceuticals.
- "Use of cDNA microarray technology at the National Institute of Environmental Health Sciences: The Tox Chip," by Rick Paules, Ph.D., National Institute of Environmental Health Sciences.
- "Drug Metabolism, drug toxicity, carcinogenesis and disease susceptibility based on gene polymorphism," by Fred Kadlubar, Ph.D., National Center for Toxicology Research.

To read the articles, click on the titles above or, from the Center's intranet homepage, click on Divisions and Offices and then Division of Training and Development. Select Advanced Topics in Molecular Genetics from the central menu.

Sakti Mukherjee is a writer/editor in DTD.

Center Cosponsors September Workshops with PQRI, AAPS

The Product Quality Research Institute—a collaborative research endeavor involving the Center, academia and industry—will be holding a workshop on blend uniformity on Sept. 7 and 8 at the Crystal Gateway Marriott in Arlington, Va.

This is PQRI's first workshop and will address current pharmaceutical blending operations designed to provide uniform distribution of drug particles in a powder blend. In addition to drug content uniformity in the final product, blending operations can also affect certain other product attributes such as drug dissolution and tablet hardness.

Legal precedence and current regulations suggest that blend testing should be carried out for each production batch to minimize the likelihood of releasing a batch that fails to meet specifications. However, general manufacturing experience suggests that, for most powder blends, blend testing for every production batch may be unnecessary.

The workshop is an opportunity for industry to provide input on the blend uniformity research and to identify other areas or issues that need to be addressed.

The mission of PQRI is to conduct research to generate scientific information to support regulatory policy. More information on the workshop, registration and PQRI's other activities can be found at http://www.pqri.org.

CDER will be cosponsoring a training program on the Biopharmaceutics Classification System with the American Association of Pharmaceutical Scientists on Sept. 25 at the Crystal Gateway Marriott in Arlington, Va.

The training will focus on the recently issued guidance, *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms based on a Biopharmaceutics Classification System.*" The workshop will examine using the guidance in applications for investigational new drugs, new drugs, generic drugs and supplements.

The BCS is a new drug development tool that allows assessment of the relative contribution of three major factors governing drug absorption from immediate-release solid oral dosage forms: dissolution, solubility and intestinal permeability. FDA's guidance expands the regulatory application of BCS and provides a general approach that can be used by sponsors and applicants to justify their requests for waiver of *in vivo* bioequivalence studies.

The workshop will feature experts from academia, industry and FDA who will discuss the theoretical foundations of BCS, methodology for classification and regulatory application. Representatives from both innovator and generic industries who have already utilized the BCS approach will provide case studies on how it has been applied and the challenges encountered.

The BCS approach offers opportunities for manufacturers to build quality into their products and to reduce unnecessary testing in humans. It will also help save time both in the drug development and drug review processes.

Additional information on the workshop and registration can be found at http://www.aaps.org.

EEO CORNER

CDER Mentors Recognized At High School-High Tech Ceremony

BY GLORIA MARQUEZ SUNDARESAN

At the conclusion of the High School-High Tech Summer Program, United Cerebral Palsy Cerebral Palsy Inc. held an appreciation ceremony in Silver Spring on Aug. 4 for private and government participants in this year's program. The students came with their parents, other family members and their supervisors and mentors from work.

Gloria M. Sundaresan, CDER EEO Staff, in her remarks on CDER's third successful year in a row, stressed the importance of funding and the volunteer efforts of the mentors and supervisors who provided direct guidance to the students. She pointed out that the real stars are the students and their parents. Strong family support enabled many students to participate in the program.

United Cerebral Palsy distributed certificates of completion to the students and certificates of appreciation to the supervisors, managers, mentors and coordinators of the program. All the students spoke about their experience in their summer jobs, especially their appreciation for learning new computer skills in an actual work environment, the friendships they developed with their mentors and their gratitude to those who provided the opportunity.

Supervisors and mentors spoke about the student's contributions to their offices and how pleased they were with the performance of their students. **Iris Khalaf** and **Jennifer Henderson** both spoke of how eager and efficient their student, **Clement Jalloh,** was in the Office of Training and Communications. "We have to come up quickly with new assignments, because Clement keeps coming back for more work to do," said Jennifer.

Iris spoke in agreement with Clement's previous remark when she said, "I'm glad Clement considers us more his friends than his supervisors and he has helped us a lot at the office."

Jody Moore, Office of the Center Director, **Casey Reeder's** supervisor said: "We appreciate Casey's help in our office, and I'm glad to be a part of this good program."

> "We have to come up quickly with new assignments, because Clement keeps coming back for more work to do"
> —Jennifer Henderson

Parents praised the program coordinators and made brief comments on the positive effect the program had on their children and its benefits to other students with disabilities.

Charles McNelly, Ph.D., executive director of the local Cerebral Palsy chapter and Mary Panella, Ph.D., director of the summer program, urged continued support of the program and thanked everyone for this year's successful summer program for students with disabilities.

Tanya Abbott, a senior management officer in the Center director's office, made a comment on the HS/HT Program, "Overall, the program is good and I'll recommend it to others for next year."

Celeste Bové and **Tammy Mueller,** Office of Testing and Research, gave credit to their co-worker, **Gail Schupp**, for providing most of the supervision to their student, **Alexander Roy.** OTR Director **James MacGregor, Ph.D.,** a strong supporter of the program for the last three years, complimented Gail for mentoring Alexander and said: "Gail was the one who really gave personal attention to our student." Gail provided a style of mentoring that she tailored for Alex and brought out his best, which was reflected in Alex's one-page thank you note to Gail.

"We are very pleased with Alex," Celeste said, "and we will miss him."

Janice Newcomb, Director of the Division of Training and Development, said her group appreciated Clement's performance. "I'd rather choose him over someone without a disability," she said. "We would like to participate in this program again next year."

CDER office and division directors who are willing to sponsor students with disabilities are encouraged to take part in next year's program and should budget about $1,000 for the six-week salary. For more information please call the CDER EEO Staff (4-6645).

Gloria Marquez Sundaresan is team leader for special emphasis and diversity management in CDER's EEO Staff.

OFFICE OF WOMEN'S HEALTH

Funds Anticipated for Research Grants to FDA Scientists

The Office of Women's Health is announcing the anticipated availability of funds for research projects for fiscal year 2001. The program provides research funds for FDA scientists to evaluate significant areas of unmet needs addressing women's health in the Agency's work. The success of this program is based on the extent to which it contributes to an identifiable increase in the review of regulated products for differential health impacts of product performance on women as reflected in product labeling and regulatory guidances and rules.

Research conducted should seek to contribute to our understanding of gender differences and ways to increase our knowledge of regulated products that impact women as they age.

Within the framework of gender differences or the health status of women as they age, the office has selected these topic areas for potential scientific research projects:

- Pre-clinical models.
- Clinical models.
- Inclusion of women in clinical trials (especially older women).
- Risk assessment and risk management.
- Marketing surveillance and pharmacovigilance

If funds are appropriated, the office anticipates making awards in mid-January. Support for these projects is usually one year to two years in duration. The number of scientific projects funded will depend on the quality of the applications received and the availability of funds to support the projects.

OIT's CDER 'Walk-Around' Coming to Upgrade Your PC

OIT will be making several necessary modifications to all CDER desktop PCs in order to optimize their performance within the Center's computer infrastructure. We are doing this task in a "walk-around" deployment by visiting each PC in the Center.

We began in July and will take several months to complete the job. A qualified deployment team technician will coordinate with the OIT building leads and the focal points to schedule a time to perform the modifications. To help you prepare, OIT's Desktop Management Team will notify you three days to a week prior to someone visiting your PC.

Assuming your PC is not currently experiencing problems and has only standard products installed, we estimate the modifications will take about 40 to 45 minutes per PC. These modifications have been tested against the standard CDER desktop software and hardware configuration. Modification times for PCs that contain non-standard hardware or software may vary.

Please contact the Help Desk (HELP) with any questions concerning the Walk-Around.

Microsoft Exchange Preparation

The migration to Microsoft Exchange is challenging and resource intensive. Here in OIT, we are devoting significant time and energy to prepare for the migration. Since we are concentrating our efforts on the migration, we will not be upgrading Russell Calendar Manager or TeamLinks. This will enable our technicians to devote the time necessary to set up and learn the new system and at the same time maintain our current systems with the same level of support you have come to depend on.

During this upcoming migration there are things that all CDER employees can do to ease this transition. One of the most important things is to clear out e-mail messages from your mailbox that you no longer need.

With Exchange, like most e-mail systems, you will have a quota on message storage space. Now is a good time to get in the habit of managing your message storage space. Managing message storage space means:

- Deleting messages that you don't need.
- Periodically checking and cleaning out mail folders.
- Breaking the habit of using e-mail for document storage.

We think that by including these small changes into your daily routine, you will help insure a smooth transition for all of CDER.

Please contact the Help Desk (HELP) with any e-mail or calendar questions.

September IT Training

(All training in Corporate S-400 unless otherwise noted.)

Monday	Tuesday	Wednesday	Thursday	Friday
				1 **DFS 2.0 Demo** MPN I, 259 10:00-11:00
4	**5**	**6** **CDER Standard Letters** 9:00-12:00 **DFS 2.0 Demo** MPN II Conf. Rm. B 10:00-11:00	**7** **DFS 2.0 Demo** CORP, S-400 1:00-2:00	**8** **DFS 2.0 Demo** PKLN, 13B-39 10:00-11:00 **DFS 2.0 Demo** WOC II Conf. Rm. G 2:00-3:00
11 **Intro. PowerPoint** 9:00-12:00 **PowerPoint Charts** 1:00-4:00 **DFS 2.0 Demo** PKLN, 13B-39 2:00-3:00	**12** **DFS 2.0 Demo** WOC II Conf. Rm. G 11:00-12:00	**13**	**14** **DFS 2.0 Demo** CORP, S-400 10:00-11:00	**15**
18 **Creating PDF Documents** 9:00-12:00 **MS Project for CDER P.M.s** 1:00-4:00	**19**	**20** **NEST** 9:00-12:00 **DFS 2.0** 1:00-4:00	**21** **Intro. Access** 9:00-12:00 **Access Queries** 1:00-4:00	**22** **Access Form Design** 9:00-12:00 **Access Report Design** 1:00-4:00
25 **CDER Letters** 9:00-12:00	**26**	**27**	**28**	**29**

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

Help Desk FAQ

Q: I get the message "No Active Document" when I close a file in Adobe Acrobat 4.0. Is there a way to fix this error?

A: Yes. In order to avoid that error message, you need to install the latest Acrobat plugins from the OIT Web.

To update your Acrobat plugins:

- Go to the OIT site at http://oitweb.
- Click on OIT Desktop Solutions in the left frame.
- Click on Software in the left frame.
- From the list of software, click on Adobe Acrobat.
- Click on Acrobat 4.0.
- Click on plugins.

An MS-DOS window will appear and then close or display the word "Finished" when the files are installed.

If the window does not close automatically when the finished message appears, close the window manually.

Please contact the Help Desk (HELP) with any questions about Adobe Acrobat.

New Version of Division Files System Scheduled for October

By Melissa Chapman and Janet Gentry

Version 2.0 of the Division Files System is scheduled for release in in early October. The DFS Working Group completed requirements in February. Subsequently, the DFS Project Team worked to meet each requirement through additional code development in DFS and through upgrades of the DFS architecture to meet the high performance and high reliability standards requested by the working group. Each user requirement has been mapped to DFS modules or to hardware improvements to ensure quality.

To facilitate changes in the business process, the Division Document Room Working Group has been meeting to discuss how the process can be streamlined in conjunction with the implementation of DFS. The DFS training available through OIT is being modified to reflect the new functionality in version 2.0.

New Functionality

One major new function in this release is the automatically generated electronic signature page appended to the PDF version of documents checked into DFS. This final page will serve as the official signature of a document. There will also be creation of electronic distribution lists. For NDA, IND, and Supplement letters the distribution list will match the one currently created when the letters are created through the CDER Standard Letters System.

For all other types of correspondence the user will have the ability to create and modify electronic distribution lists. To facilitate data entry, the appropriate division document room will always be a mandatory entry on all electronic distribution lists. Once a document is in final form a copy of the document or a pointer to the document will be sent electronically to the recipients designated on the distribution list. When division document room staff receive the copy of the document, they will perform the appropriate data entry into the COMIS/NDE database.

In addition, the DFS 2.0 release will provide improved searching capabilities and the ability to designate multiple authors.

Rollout Process

The OIT Walk-Around project is performing the key desktop upgrades needed for the DFS 2.0 rollout (page 8). The deployment of the upgraded DFS 2.0 software will happen automatically when you log onto the system. Other software will be loaded on the DFS server. This means that the DFS 2.0 software will be available to all DFS users simultaneously. The Center director's office will be sending an e-mail in early September designating the use of DFS 2.0 in review divisions.

Since DFS will be required for routing documents, facilitating data entry into COMIS, and for archiving, it is imperative that users validate DFS functionality. There will be a parallel paper and electronic process for approximately 60 days after the DFS 2.0 rollout. This means that the current paper process for routing reviews and communicating with the division document rooms will continue concurrent to the implementation of the electronic DFS process. This time period will be used to gauge the accuracy of the electronic process and validate that the paper process can be eliminated.

Demonstrations

Look for these upcoming 1-hour demonstrations of DFS 2.0 in your building:

- *Corporate Boulevard, Room S-400:* Aug. 30, 10 a.m.; Sept. 7, 1 p.m.; Sept. 14, 10 a.m.
- *Metropark North I, Room 259:* Sept. 1, 10 a.m.
- *Parklawn, Room 13B-39:* Aug. 29, 10 a.m.; Sept. 8, 10 a.m., Sept. 11, 2 p.m.
- *Woodmont II, Conference Room G:* Aug. 28, 1 p.m.; Sept. 8, 2 p.m.; Sept. 12, 11 a.m.

The OIT point of contact is **Melissa Chapman** (CHAPMANM).

Melissa Chapman is a supervisory computer specialist, and Janet Gentry is a computer specialist in OIT.

CASE to Hold Workshop on 'Quality of Life' Measures Sept. 28

By Judith A. Racoosin, M.D., MPH

A one-day workshop for reviewers addressing health-related quality of life measures will be held Sept. 28 in the Advisor's and Consultants Conference Room at 5630 Fishers Lane from 8 a.m. to 5 p.m. The Committee for Advanced Scientific Education is sponsoring the event.

Health-related quality of life measures usually refer to patients' subjective judgments about their physical, social and mental well-being. They differ from endpoints currently accepted by FDA in clinical studies that rely on objective measures of morbidity and mortality, such as disease progression or death.

In recent years, the pharmaceutical industry has proposed that health-related quality of life claims be permitted in product labeling and advertising. The industry contends that such claims are scientifically sound because they are supported by assessments used in adequate and well-controlled clinical trials.

The workshop will introduce reviewers to health-related quality of life assessments and describe how they are designed, validated, analyzed and interpreted.

General criteria by which such claims may be considered for inclusion in product labeling will also be addressed.

You can sign up for the workshop by selecting the on-line registration button on the Division of Training and Development's CDERnet site at http://cdernet.cder.fda.gov/dtd/index.htm.

Judith A. Racoosin is a safety team leader in DNDP and a CASE member.

FDA Ethics Intranet Site

FDA's Ethics Staff has developed an intranet site to provide information on their programs and services. Subjects covered include the purpose of FDA's ethics program, prohibited financial interests, outside activities, financial disclosure reporting and post-employment policies.

The site, which also includes sections for comments and frequently asked questions, can be found at http://learnfda.fda.gov/ohrms/ethics/ethics.htm.

1st Medication Guide; Synthetic Thyroid Hormone NDA Approved

FDA on Aug. 24 announced it is requiring pharmacists to issue a medication guide—FDA-approved patient labeling—when dispensing alosetron hydrochloride (Lotrenox). The guide will help ensure that women using the prescription drug to treat the diarrhea-predominant form of irritable bowel syndrome will understand the rare but serious risks of alosetron and how they can recognize those risks and take early action to prevent serious harm. These risks include complications from constipation and the risk of ischemic colitis, a serious complication caused by reduced blood flow to the intestines.

Information for health professionals who prescribe alosetron has also been updated. Alosetron is a drug with a demonstrated benefit in the treatment of diarrhea-predominant IBS, which can be severely incapacitating. FDA believes that the benefits of alosetron outweigh its risks when it is used according to the instructions in the medication guide, which reflect the revised professional labeling.

Alosetron is the first drug to have a medication guide under regulations that became effective in 1999. A medication guide contains FDA-approved information, written especially for patients, that pharmacists are required to distribute with products that FDA has determined pose a serious risk and for which patient labeling can help prevent that risk. In some patients, the risks associated with alosetron led to hospitalization or surgical procedures not normally associated with IBS.

Between the approval of alosetron on Feb. 9 and June 1, FDA received seven reports of serious complications of constipation. This resulted in the hospitalization of six patients, three of whom required surgery. While 25 percent to 30 percent of patients taking alosetron in the pre-approval clinical trials had experienced constipation, FDA had received no reports of serious complications before approval.

During the same time period, FDA received eight reports of ischemic colitis in patients taking alosetron. This resulted in four hospitalizations, four endoscopic procedures and no surgeries. In addition, four cases of ischemic colitis were reported in the clinical studies of alosetron before approval. All 12 patients with ischemic colitis recovered without serious consequences when alosetron was discontinued.

Alosetron's sponsor, GlaxoWellcome of Research Triangle Park, N.C., issued a "Dear Health Care Professional" letter to inform prescribers of the labeling changes and a "Dear Pharmacist" letter to inform pharmacists of their obligation to provide patients a medication guide with each alosetron prescription filled.

More information is on the Center's Lotrenox Information Page at http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm.

On Aug. 21, FDA approved the first single-ingredient levothyroxine (T-4) sodium product (Unithroid). Levothyroxine had been marketed in the United States since the 1950s without an NDA, apparently in the belief that it was not a new drug based on its similarity to pre-1938 thyroid extract products.

In the *Federal Register* of Aug. 14, 1997, FDA discussed new information on these products showing significant stability and potency problems and called for NDAs. These problems have resulted in product recalls and have the potential to cause serious health consequences to the public.

After Aug. 14, 2001, all marketed levothyroxine products will be required to have approved applications. New applicants may now file generic drug applications using Unithroid as the reference listed drug.

Levothyroxine, identical to a natural thyroid hormone produced by the body, is most commonly used to return thyroid hormone levels to normal in patients with hypothyroidism. The dose of levothyroxine for replacement or supplemental therapy in patients with hypothyroidism must be individualized based on patient response.

With the approval of Unithroid, patients and physicians will now have an oral levothyroxine sodium drug product that has been determined to be safe and effective by the FDA and that also meets FDA standards for manufacturing processes, purity, potency, and stability.

Unithroid is manufactured and distributed by Jerome Stevens Pharmaceuticals of Bohemia, N.Y.

For more information, see the Center's Unithroid Information Page at http://www.fda.gov/cder/drug/infopage/unithroid/unithroid.htm.

Budesonide inhalation suspension (Pulmicort Respules) for asthma in children between the ages of 1 to 8, received FDA approval on Aug. 8. The product is the first anti-inflammatory corticosteroid formulated for inhalation using a nebulizer in this age group.

Previously, no other inhaled corticosteroid has been approved for use in children younger than 4 years of age. This approval allows for treatment with an approved formulation in a significant, currently unserved pediatric asthma population.

Inhaled corticosteroids when used as maintenance therapy are effective in reducing the inflammation that often precipitates an asthma attack or bronchospasm. Improvement in asthma control following treatment with the budesonide product can occur as early as two weeks, although the maximum benefit may not be achieved for four to six weeks after starting treatment.

Approval for the drug was based on three randomized U.S. studies of 12-weeks duration in more than 1000 patients aged six months to eight years of age. The children studied had persistent asthma of varying duration and severity.

Studies have shown that inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients.

In clinical studies with a variety of inhaled corticosteroids, the mean reduction in growth velocity was approximately one centimeter per year and appears to be related to dose and duration of exposure. The potential for catch-up growth has not been adequately studied.

The AstraZeneca Group located in Wayne, Pa., manufactures Pulmicort Respules.

LePay: DSI Works to Help Relieve Pressure on Overworked IRBs

By Sherunda Lister

'I think an informed consumer is an extremely invaluable factor in ensuring clinical trial success as well as human subject protection," said **David LePay, M.D., Ph.D.,** Director of the Division of Scientific Investigations on detail as Senior Advisor for Clinical Science in FDA's Office of Clinical Science.

Dr. LePay will serve as acting director of the newly established office located within the Office of Science Coordination and Communication. As acting director, Dr. LePay said that a big part of his job will be to develop the office as far as its responsibilities and its interactions with other parts of the Agency as well as outside stakeholders.

Human Subject Protection

Protecting human subjects is a major concern with any clinical trial. So is ensuring that trial recruitment does not exploit any one population. That's why Dr. LePay feels that each patient's understanding of informed consent and taking the time to be fully informed are important. "That to me is the greatest control in the system," he said. "That's something that we try to do a great deal of from DSI. Our outreach is to work with communities as well as to work with clinical investigators to talk about these issues. What are the controls in place? What should you be asking about clinical trials? We have done this in many forums. But our regulations clearly do provide that there be no coercion of subjects."

IRB Oversight

Recent events have focused attention on IRB performance measures and how the Agency can establish that these groups are in fact doing the job of protecting human subjects. Additional duties for Dr. LePay on detail will include working on areas dealing with oversight of human protection identified by the HHS Inspector General's Office, the National Bioethics Advisory Committee, our own constituencies and the department's new Office of Human Research Protection, formerly the NIH Office of Protection from Research Risks.

Dr. LePay said that there were several issues raised by the groups. The IG report, for example, deals with very basic issues about investigational review boards—the way they are set up, how they perform and do they really protect human subjects. "We have a system in place, and we believe that it works. But some of their concern is, in fact, how do we prove that they are protecting human subjects," said Dr. LePay, "you can't always prove the negative."

There are also operational issues related to IRBs, such as IRB registration. CDER abstracts information about the boards from clinical investigator forms. According to Dr. LePay the other centers do not have a comparable system in place and get their information from investigator's statements or through other means. "There is not a systematic approach that now exists to acquire a whole inventory of IRBs that are across the board doing FDA-regulated studies," said Dr. LePay. "There may even be loopholes, and I expect there are."

FDA Outreach to IRBs

Outreach to the IRB community is also a concern. How do IRBs train their members? How do IRBs work with clinical investigators? How can FDA work with them to establish consistent operational standards? How much training do board members need? These are all things that need to be addressed according to the IG report.

Another major concern, Dr. LePay said, is how overburdened IRBs have become. "The process has become very strained. We need to make sure IRBs stay focused on what their real job is—ensuring the ethical conduct of clinical trials. In the FDA system, the day-to-day monitoring of studies is the responsibility of the industry or other sponsor. That needs to be spelled out better. IRBs are being asked by their institutions and others to take on more responsibilities that are overburdening them. We may need to clarify with IRBs what we expect of them."

As for what is causing the overburdening, Dr. LePay feels it's a combination of things including how institutional review boards are being funded and how they are staffed. "IRBs are being staffed by individuals who have multiple commitments—they may be clinical investigators themselves, researchers, administrators. For those members who sit on the IRB, this is just a fraction of what their basic job is in an academic institution. These are largely people who are volunteers within their own institutions and are doing this as just a portion of their overall responsibilities."

Commercial IRB Issues

Some sponsors have chosen to use central or commercial IRBs as an alternative; and this is not a violation of FDA regulations. According to Dr. LePay: "The stipulation in the regulation, though, is if you are going to use a commercial IRB, there are considerations about conflict of interest. You have to be very 'in tune' to potential conflict-of-interest problems. In a commercial venture, you have to be careful that there are controls between the administrators and the reviewers so that money does not become a consideration."

Local oversight is also required when working with a commercial or central IRB. "We have to be sure that commercial IRBs or central IRBs have some level of local oversight. That's required by law."

For example, a sponsor can have an IRB in California even though it is conducting the study in New York. But, said Dr. LePay, "That California IRB has to, under regulations, provide that there is some form in which they are familiar with local conditions, ethics, and community attitudes."

He also pointed out that there are good and bad IRBs—both commercial or institutional. One is not necessarily better than the other.

Overall, Dr. LePay expects that the new FDA Office of Clinical Science will be able to work effectively with the IRB community and "to speak with them forthrightly about where potential areas for regulatory improvement can take place."

To accomplish this, the office will work cooperatively with the department, the Office of Human Research Protection and the FDA's centers and Office of Regional Affairs. "That's really the hope of this new office—that it will be in a better position to coordinate these policy issues and directions that the Agency will take in clinical trial conduct and oversight."

Sherunda Lister is a public affairs specialist in the Office of Training and Communications.

FDA Seeks Comments on ICH Common Technical Document

(Continued from page 1)

authorities in the three ICH regions, the United States, Japan and the European Union.

To make handling and commenting on the guidance easier, it is broken into four parts. The first is a brief overview (M-4) of the modular structure of a submission. There are three detailed parts for quality (M-4Q), or chemistry and manufacturing controls information; safety (M-4S), or non-clinical information; and efficacy (M-4E), or clinical safety and efficacy information

In its final form, the M-4 common technical document will:

- Reduce the time and resources used to compile applications.
- Ease the preparation of electronic submissions.
- Facilitate regulatory reviews and communication with sponsors.
- Simplify the exchange of regulatory information among regulatory authorities.

The document addresses the organization of information and appropriate format for data presented in new drug applications. "There are always application-to-application variations in NDAs, but new applications prepared with this guidance will hopefully be somewhat more uniform in format and not dissimilar to what we receive now," said **Robert DeLap, M.D.**

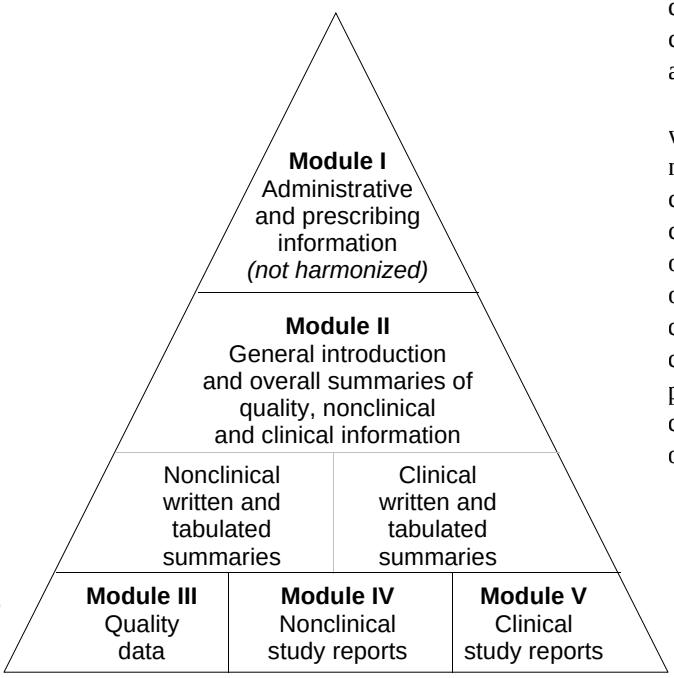
The common technical document will be the standardized part of a submission for new drugs, presented in a modular fashion with summaries and tables.

One of the modules, Module I, is reserved for specific regional requirements such as application forms and labeling. Module I won't be harmonized.

A submission that follows a final guidance for the common technical document will have the modular structure illustrated in the pyramid graphic below.

The four modules are:

- *Module I.* Administrative and prescribing information, such as the application form and product labeling.
- *Module II.* An overall table of contents and structured summary information and tables.
- *Module III.* Quality table of contents and data.
- *Module IV.* Nonclinical table of contents, study reports and key literature references.
- *Module V.* Clinical table of contents, study reports and key literature references.



Modular Structure of ICH CTD

For the nonclinical information, Module II uses a different organization. Module III contains the studies, which serve as the primary basis for review, and "is organized as in the past and should not alter the reviewer's ability to conduct a review," said **Joseph DeGeorge, Ph.D.**

Module II begins its information presentation with a one-page executive summary of the drug, including its pharmacological class, mode of action and its proposed clinical use.

Next are the overall summaries for quality in about 40 pages and nonclinical and clinical summaries in about 30 pages each.

Finally, there are more detailed written and tabulated summaries of nonclinical information and a clinical written summary. The nonclinical summaries discuss pharmacology, pharmacokinetics and toxicology. The clinical summary discusses biopharmaceutics and associated analytical methods, clinical pharmacology, clinical efficacy, clinical safety and provides synopses of individual studies.

Technical contacts are:

- **Joseph J. DeGeorge, Ph.D.,** for the safety (nonclinical) components.
- **Charles P. Hoiberg, Ph.D.,** for the quality components.
- **Robert J. DeLap, M.D.,** for the efficacy (clinical) components.

FDA Officials Spend up to 3 Days on Road Reaching ICH Brussels Meeting

(Continued from page 1)

ical Trials (E-10) and *Clinical Investigations for Medicinal Products in the Pediatric Population (E-11).*

They approved two guidances for Step 2 regional consultation: *Good Manufacturing Practice for Active Pharmaceutical Ingredients (Q-7A)* and minor revisions to *Impurities: Residual Solvents (Q3C).*

The pharmacopoeias in the regions and an ICH expert working group agreed on harmonization of Microbial Limit Tests, one of the remaining general chapters of the three pharmacopoeias.

The steering committee received a report from a "brainstorming" meeting on developing an ICH topic on gene therapy.

The MedDRA management board reported good progress on implementation of the 0medical terminology dictionary in the three regions. They also reported that they will make some structural changes in the terminology to improve quality.

The future of ICH, including possible new topic areas for future harmonization, implementation, monitoring and maintenance procedures, and the structure beyond ICH 5, were discussed. These discussions will be continued in San Diego.

The ICH Global Cooperation Group held its third meeting and presented a paper on principles of cooperation and Qs and As on ICH that they hope to publish on the ICH Website.

Justina Molzon is the Center's Associate Director for International Affairs.