

CDER Priority-Setting Meeting

August 17, 1998

Summary of Proceedings

Agency Presentations

FDA: Linda Suydam, Associate Commissioner for Strategic Management, said FDA was undertaking the stakeholders' meetings with great enthusiasm and hoped to get input on all six objectives: (1) maximizing the availability and clarity of information about the review process; (2) maximizing the availability and clarity of information for consumers and patients about new products; (3) implementing inspection and postmarket monitoring provisions in the Modernization Act; (4) ensuring access to necessary scientific and technical expertise; (5) meeting application review time periods by July 1, 1999; and (6) eliminating review backlogs by January 1, 2000.

Ms. Suydam identified seven issues of concern: (1) adverse event/injury reporting; (2) product safety assurance; (3) product application reviews; (4) food safety; (5) outreach; (6) scientific infrastructure and research; and (7) tobacco. She cited the recent JAMA article that speaks to many thousands of unreported injuries and said that means the FDA needs to focus on adverse event reporting and product safety. User fees have enabled the agency to meet goals for product application reviews. Food safety is a presidential initiative and will require increased focus from FDA. The agency needs more input from its stakeholders. Scientific infrastructure has been neglected while the agency has focused on priority programs. FDA's tobacco initiative is uncertain in the light of the recent appellate court decision.

From 1993 to 1999, the FDA's budget has grown from \$800 million to \$1.26 billion. That looks impressive, she said, but inflation erosion and dollars mandated for priority programs create a substantially under-funded workload. Priority programs include user-fee supported application reviews with a mandated level of appropriated fund support, the mammography quality screening program, tobacco, and the food safety initiative. As a consequence of mandated programs, support for the agency's other program areas has fallen over the six-year period from \$671 million to \$586 million.

CDER: Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research (CDER), discussed the current state of the U.S. drug regulatory system. The center faces a myriad of tasks and expectations, and its stakeholders are never in agreement. It is important for stakeholders to see other priorities in the drug regulatory system. The key

issue is how to prioritize in face of limited resources and how to get the best possible results. The system has been in evolution during most of the 20th century. Its mission is to promote and protect public health by assuring that safe and effective drugs are available to Americans. The most recent modifications are in the Modernization Act. Agency components of the drug regulatory system include: CDER, ORA, Office of the Chief Counsel, and Office of the Commissioner. Outside the FDA, key components include state and local officials, state licensing boards, IRBs, and the DEA.

Expectations for the system are that: all marketed drugs are effective and safe in the context of their use; human drugs are of high quality; generic competition will keep prices down; advertising and promotion of drugs will be informative and not false or misleading. New expectations in this evolving system are access to experimental therapies and information about drug use targeted to individual groups such as children and the elderly. Americans expect a robust drug development program that protects human subjects.

Dr. Woodcock outlined the processes that help meet these expectations: application review; standard setting; post-marketing safety surveillance; compliance and enforcement activities; research; policy development; international collaboration; communication with stakeholders; information management; and training that is collaborative with industry. To support these processes, there are about 2,500 people in drug regulation at FDA, 1,700 at CDER and about 850 in ORA. The budget for drug regulation totals about \$284 million with \$206 million for the center. A large portion of the budget goes to application review. Priority setting includes historical practices and direct statutory mandates, for example, PDUFA dictates a baseline level of effort in premarket review. Advocacy plays a role in setting priorities; she cited orphan drugs and AIDS as good examples.

Dr. Woodcock then discussed the performance of the processes. The investigational new drug process is well managed and timely. There is a fair amount of guidance for people who do drug development; however, there can be improvements for specific indications. The IRB system is under a lot of stress right now. Shortening the drug development time can't be done without research. New drug review used to take a lot of time. Now, with user fees, it is a very timely program. It is increasingly open and transparent with more than 50 advisory committee meetings per year. Standards are controversial in some areas, such as: requirements to study children, women, elderly, ethnic groups; antibiotic resistance; and over-the-counter switches. Drugs to be used for chronic conditions present challenges on how much information the FDA should compel and how long it should require follow-up on patients.

Drug safety is a hot topic, and people seem to think it relates to review. How many people should be studied is an important question. The center struggles with the issue of the benefits to the many versus the risk to a few. Drugs may benefit many, but a few people may be seriously and unavoidably damaged. Where is the point when the risk to the few becomes unacceptable, she asked. Drug-drug interactions present similar concerns.

The generic drug application program is performing very well. More than 50 percent of the reviews are performed within the statutory limit of 180 days. The time from approval

to market has dropped from 40 months in 1993 to 19 months. The number of generics approved has gone up. Manufacturers and Congress want even better performance. Also, there are concerns about barriers to generic competition. A thorny scientific issue is how to determine bioequivalence for drugs that are not pills.

The guidance on the New Use Initiative tells manufacturers what they need to do and how much data they need to bring in a new use. A draft guidance for new uses for cancer drugs aims at getting many off-label uses approved.

Product quality assurance needs stakeholder input. Consumers need to know that a product is going to work. FDA has put a tremendous effort into assuring quality of marketed drugs. That shouldn't be a worry if a consumer is sick. Quality can come at a high cost. So FDA is working with industry to make quality available at reasonable cost. Maintaining adequate inspection coverage in the United States is a concern. Right now, FDA is not meeting its two-year requirement. Third-party audits are a suggestion as well as first-party audits. A second issue is inspection of foreign establishments. How can FDA be in those establishments every two years, she asked. One method is mutual recognition if the agency can be sure that foreign inspections get the same result. The FDA will be working on mutual recognition of inspections and international standards for bulk pharmaceuticals. The agency is attempting to develop a regulatory scheme that will permit pharmacy compounding and maintain quality.

In regard to surveillance and compliance, Dr. Woodcock observed that the agency does not put a large amount of resources into health frauds unless they endanger health. Dietary supplements have a separate system. The marketing of unapproved drugs that have escaped the system is also not given a high priority unless there is a health risk.

Drug marketing and advertising surveillance is vigorous and adequate, but there are issues that need to be resolved. The center is interested in input on direct-to-consumer advertising and dissemination of reprints about off-label uses. There is a great deal of interest in having consumers receive prescription drug information at the pharmacy. They need correct information. How pharmaceutical firms fit into the managed care scheme, promote their drugs and influence switches is also a concern.

Human subjects in clinical trials need protection. The agency audits clinical trials and IRBs. More training of IRBs is called for by the Institute of Medicine. Who is going to do that, she asked, and how is the quality of foreign clinical trials going to be brought up to U.S. standards.

On the safety of marketed drugs, she said that everyone has to be aware that pre-marketing testing can't detect all problems or toxicities. Some events are rare. Some problems are caused by use outside of approved parameters. Sometimes medication errors are encountered that were hard to anticipate. So there is a need for a vigorous program to detect these problems. The agency receives about a quarter million adverse event reports per year. The center is totally computerizing this and moving to electronic submission of adverse event reports. That is a passive reporting system. The center would be interested

in comments on a more active system. She said the center thinks it would be of benefit to have additional kinds of surveillance. Effective communication is linked to drug safety. If the center can get out information about problems with drugs, then they are safer. This is an important priority for the center.

Dr. Woodcock said the center would like to have drug development statistics and is always asked about them. The center would like to have drug statistics similar to CDC's health statistics. It is important to develop this information.

She cited the need to do communications research. For example, the pregnancy categories are leading people to make inappropriate decisions. The only way to change them is to go out to see how people actually respond to different versions.

In summary, she said the drug regulatory system in the United States is very effective and performing well. There are many expectations for improvement and competing priorities. The center needs to hear from stakeholders.

Stakeholder Presentations

Panel A

American Pharmaceutical Association (APhA): John A. Gans, Pharm.D., identified key areas for his organization which represents 190,000 of the nation's pharmacists:

- *Need for a new classification scheme for prescription drugs*: Economic pressures force physicians to spend less time with patients and prescribe drugs with which they may be unfamiliar. There should be a classification for high-risk drugs with special or unusual risks that call for closer monitoring by physicians and patients.
- *Drug marketing and advertising*: Distribution of free samples is outmoded, undermines the few safeguards in the existing system and deprives the patient of pharmacist counseling. There is a need for a mechanism for starter doses that uses the standard distribution system. Gans expressed concern that DTC advertising has the effect of asking physicians to prescribe outside their zone of familiarity. He called for research to see if this is increasing adverse events and asked CDER to review the policy. He asked that legislation permit manufacturers to distribute information on unapproved uses to pharmacists as well as physicians. Pharmacist counseling is very different depending on intended use. He welcomed the draft guidance on marketing by health care organizations on behalf of manufacturers. He said it is essential for CDER to keep health care formularies from becoming inflexible tools of drug marketing.
- *Post-marketing surveillance*: On the eve of many more pharmaceuticals becoming available that act on more molecular systems, the current passive system is inadequate to identify adverse effects and problems with inappropriate prescribing or use. Gans said that advances in information technology available to many of his groups' members can develop valuable data and volunteered to work with the center on this issue.

- *Recalls.* Pharmacists have difficulty receiving timely notification, and his group would be willing to work with the center on using the latest technology to inform pharmacists about drug product recalls or safety changes.

Association of Food and Drug Officials (AFDO): Cynthia T. Culmo, R.Ph., said her group supports position that FDA is performing well. Her suggestions represent the concerns of state and local regulators.

- *Drug marketing and advertising:* The best method to exercise oversight would be to use consumer panels. The review should be prior to the advertising.
- *Inspections:* The relationship between CDER and the field needs to be clarified for local officials. CDER-directed inspections are product specific and not comprehensive. Culmo pointed out that some inspections are directed to the regulation and not the health impact of the regulation. She questioned, for example, the need for process validation at some small firms that make a single, simple product. She expressed concern about ensuring that foreign products are the same as U.S. products. Foreign countries need more oversight, and she suggested that the FDA could devote its resources to foreign inspections while contracting with states for domestic inspections. The mutual recognition agreement is attempting honorable and desirable results, but foreign countries need to have not only equivalent standards but also effective regulatory programs.
- *Drug information:* Validation of drug information on the Internet is a concern. The placement of FDA articles in professional and medical journals, consumer magazines, and health and trade magazines would be helpful as would information in doctors' offices, hospitals and emergency rooms. An FDA Internet site would be an effective way of providing information. She called for improved access to package inserts for regulators and the public.
- *Surveillance and adverse event reporting:* CDER should emphasize decreasing adverse events and secondarily concentrate on the passive reporting system. Improved information will help avert many adverse events. There should be increased effort to rapidly remove harmful drugs from commerce. The center should consider mandatory drug reporting by hospitals for ADEs, similar to that for devices. Safety information notices need to be provided on a continuous basis and not just at the time of first notification.
- *Balance:* Premarket review should be emphasized. Postmarketing surveillance could be strengthened by using state resources and mandatory reporting.
- *Priorities:* CDER should place its highest priority on premarket review. Expedited removal of unsafe products is critical. OTC monographs needs to be finalized, and review of grandfathered drugs like ephedrine need to be done. Imports continue to be a problem. Personal use import exemption policy needs to be looked at, especially the potential for diversion into normal commerce.

Pharmaceutical Research and Manufacturers of America (PhRMA): Bert Spilker, Ph.D., M.D., presented condensed comments with details and substantiation submitted to the docket.

- *Drug marketing and advertising:* PhRMA applauds FDA's new policy on DTC advertising. Ads empower patients, prompt patients to seek help, promote patient-doctor exchange, and reach underserved populations. A recent *Prevention* magazine survey shows DTC advertising promotes public health by encouraging patient-doctor dialogue and health-seeking behavior. FDA's question about ensuring appropriate messages in drug advertising overstates the responsibility and authority of the FDA.
- *Inspections:* CDER should take a more comprehensive approach in managing and coordinating GMP compliance inspections. He called for a more collaborative effort with industry aimed at an effective and efficient program. He submitted detailed recommendations.
- *Drug information:* Health care providers need access to the latest information. Dissemination isn't promotion. It is appropriate for research pharmaceutical companies to provide information on peer reviewed research since they are the most knowledgeable. FDA should ensure that regulatory limits are minimally intrusive and consistent with the Constitution and the Modernization Act.
- *Surveillance:* He made five points: (1) Safety is important to companies, and they have extensive systems in place to monitor the safety of products and report to the FDA. (2) Current safety standards are significantly higher than in past. Since greater numbers of patients are studied for each NDA, the safety data has risen. (3) Slowing the drug approval process would harm public health. (4) FDA and industry must educate others about the vast amount of safety mechanisms in place. (5) To the extent the system can be improved, industry will work with others to achieve that goal.
- *Priorities:* More interaction and collaboration is desirable. CDER should avoid issuing guidances that don't take into account useful perspectives that can be provided by industry.

ALS Association: Hiroshi Mitsumoto, M.D., described the neurodegenerative disease and said that FDA has been helpful and is committed to helping the association. His comments concerned question six, priorities. His group believes there is no higher priority than rapid development and review of drugs for serious and rapidly fatal diseases such as ALS. His group is hopeful that proper implementation of fast-track provisions of the Modernization Act will expedite drugs for serious and life-threatening disease. FDA needs greater authority to approve drugs that strongly suggest effectiveness and obtain substantial evidence through confirmatory phase IV trials. The need for placebo controls in Phase III studies of diseases that are relentlessly progressing needs to be reassessed. If two studies show safety but only one shows minimal efficacy, then the drug should be approved. In a disease such as ALS, long-term exposure to relatively safe agents isn't an issue. ALS has not been treated equally with cancer and AIDS. Advisory panels need true experts. The

ALS community feels that there are no true ALS experts on advisory panels; although, nearly all ALS experts are involved in research and have ties to pharmaceutical companies. He suggested international experts. He was critical of different requirements between CDER and CBER concerning the number of confirmatory trials required. FDA should schedule patient testimony at advisory panel meetings after presentation of data. Presenting highly emotional testimony first impairs rational judgment and denies patient groups the opportunity to view the data. FDA should fund new research for finding surrogate markers.

Panel A Discussion

Dr. Woodcock mentioned that CDER and CBER have issued a joint statement on efficacy standards so there should be no more differences.

Ms. Culmo was asked to amplify her comments on inspections. She said most of the concerns came from small companies in California and Texas. She reported that on joint inspections the FDAer goes exactly by the regulations. FDA wrote up a firm for a process validation error, but it wasn't clear that it would be needed for the simple product the firm produced. She said there is confusion where direction comes from—CDER or the regional office.

Dr. Lumpkin pointed out that CDER's drug surveillance systems were never designed to be a registry, but served the purpose of identifying rare, serious adverse events. He asked if a system is needed to capture statistics on adverse events. He asked if APhA and AFDO had systems to capture this data and could it be shared with CDER.

Dr. Gans replied that they would like to get more statistical information. Rapid approvals don't give the time needed. He mentioned new practices in pharmacy such as Project Impact, which has enrolled 700 patients, and 25 pharmacies in 15 states that allow a finger stick to check blood lipids. Dislipedemia is a challenging disease for compliance because it has no symptoms. His group believes this project will be an important data source. Pharmacists are becoming actively involved. Sometimes products are lost because they are used inappropriately, for example, Duract. A system that would block patients from obtaining a refill until a liver test has been performed, may have solved that problem. Pharmacists are at the beginning of evolving more sophisticated systems.

Ms. Culmo added that statistics would be useful to her organization. Her group supports required reporting. The biggest criticism of a passive system is the lack of a denominator, she said. In Texas, six interlinked poison control centers provide a lot of information that other states can't access.

Dr. Spilker agreed that for important, specific questions, the resources to get the answers should be made available. He said it isn't necessary to collect statistics on the whole world

of pharmaceuticals. A decision needs to be made about which statistics are the most important given limited resources and whether they are going to be used ahead of time.

Dr. Woodcock asked Dr. Gans to expand upon categorization of drugs and pointed out how critical it is to get out clear information. She used the example of thalidomide. Dr. Gans responded that clearly the system for thalidomide will be better than other high-risk drugs approved in the past such as Clozaril and Acutane. The system treats all approved drugs alike, and there is a huge morass once a drug is approved. Once a drug is rushed through—and he supported that for things like ALS—there is no net under them. There are going to be 30 to 40 times more sites for drug action than there are now, and one class doesn't work.

Dr. Lumpkin asked Dr. Mitsumoto for his suggestions on public input at advisory committee meetings. Dr. Mitsumoto replied that he had no good suggestions. At one meeting, testimony occurred first and then discussion. At a second meeting, the discussion was first and then testimony. He said that had he been on the panel that heard testimony first, it would have been difficult for him to make a rational decision, especially since he knew the patients. He said FDA needs to implement this important process in a scientific way rather than an emotional one.

Dr. Gans expanded on public information and the unapproved uses issue. Getting information to the patient is a huge challenge to the pharmaceutical profession. They need help from the public. The prescription blank hasn't changed in 150 years. The intended use for the drug included on about only 20 percent of prescriptions issued. Computers that can give patients information on the intended use—and that's not the diagnosis. Pharmacists would also like to know patients' ages. He asked what would a patient do when the doctor prescribes a drug for an unapproved use and the patient is given an unrelated information sheet. Pharmacists also have to work with insurance companies who won't pay for unapproved uses. Pharmacists want to be the source of information but need to know at least the intended use.

Dr. Spilker recommended more cooperation among professional societies. Dr. Williams observed that the FDA has shied away from the practice of medicine. Dr. Gans said that he wasn't recommending that the agency regulate medicine or pharmacy, only that it should be part of the dialogue.

Ms. Gray asked Dr. Spilker to expand on first party or third party audits and the conditions under which a first-party audit would be more desirable. Dr. Spilker said that companies are skeptical of the first party audit program because (1) it calls for them to share internal audit information, (2) they didn't see any benefit to the program, and (3) the approach did not involve the industry in its design. Industry is anxious to collaborate and not just react to pilot programs. He said some issues can be avoided when industry and FDA work together. Industry rarely reacts to the first-party audit program. He offered to sit down and work out a program that both could agree upon. Ms. Gray responded that the public meeting was intended to get that input.

Dr. Williams asked how the balance between state and Federal regulators could be strengthened and improved. Ms. Culmo replied that one of the ways is through contracts. She cited compressed gases and medical devices as examples. It's simplest in states that have statutes that mirror the Federal statute. It could be improved and other states included. Dr. Woodcock asked if partnering with states for domestic inspections is possible without contracts. Ms. Culmo replied that partnering already takes place in border states like Texas, California, and Florida. She said the authority and expertise lies with FDA. She felt FDA should concentrate at borders and states could do domestic inspections.

Mr. Lillie asked for elaboration on ADRs and mandatory reporting. He inquired how the managed care system might be stimulated to provide FDA better information since there is a lot of grassroots reporting occurring. Dr. Gans said that spontaneous reports are always a challenge because they are seen as a failure. He gave the example of a company that was able to contact each patient and each prescriber on a recall. Systems are there that can do that. No one seems to get blamed for a failure, but problems are there. Insurance companies are forcing pharmacists and industry to develop a fail-safe system. He said pharmacists see more of this because it fits their goal of managing the drugs for people. He felt that large insurers need to be stimulated to get information back to the company and then from the company to FDA.

Dr. Williams observed that there are problems with greater interaction in regards to the Federal Advisory Committee Act and good guidance practices. Dr. Spilker responded that it's usually resolved by getting the legal people together first.

Panel B

Consumer Federation of America: Mary Rouleau reported that her organization doesn't endorse FDAMA Section 406 as a way to hold the FDA accountable and considers it a diversion of FDA resources from consumer protection mandates. CFA bitterly opposed FDAMA and considers it a rollback. Meeting application review deadlines may take place at the expense of other activities. Minimizing deaths and injuries needs to be built back into FDA's plan. Collaboration with industry must not become sugar-coated deregulation. Drugs and devices must work and be safe. Success should not only be measured by the number of drugs and devices approved but also by the number of deaths, adverse reactions, and recalls reduced. The lack of a commissioner is appalling and indicates lack of support. The number of questions for the nominee is unprecedented in quantity and represents an effort by industry to work through senators to tie hands of the commissioner and the agency in advance. Consumer and patient groups unsuccessfully raised the issue of meeting statutory obligations on top of Modernization Act deadlines and new initiatives for food and tobacco. CFA supports user fees and asks Congress to expand them. CFA unsuccessfully fought the one clinical trial provision and fears that this will become the norm rather than the exception. Examples of fraudulent clinical trial data were brought up as examples of a problem with approvals based on one clinical trial. Both FDA and industry must ensure integrity of clinical trials and the publication processes. It's not

acceptable that post-marketing activities suffer because of premarket activities, and the agency should be adequately funded to support both fully.

National Women's Health Network: Cynthia Pearson said her group wants to see FDA remain a strong regulator. Efforts to reform must build on, not dismantle, the agency's tools. She said that the agency is finding it increasingly difficult to meet statutory obligations. She cited a quarter million ADRs and five drug withdrawals as evidence that safety is compromised. Patients now are more likely to get information from advertising and to take drugs that have been less widely tested. FDA must fully be the regulator and protector of human health. Nowhere is the need more apparent than in drug advertising. Drug companies have taken full advantage of relaxed rules. DTC advertising has skyrocketed. Consumers are getting precious little information on the safety of products in these ads. The public gets images of a drug's benefits versus its side-effects. She cited examples of misleading ads. Websites and toll free numbers are controlled by industry. Patient information sheets are written by private companies. Consumers have no way of knowing why the ad was pulled, and the damage has already been done. She cited a parallel rise in DTC ad budgets and rise in ADRs. Many argue that there is no connection. As more drugs enter on the fast track with less data, consumers will be put at risk. They are barraged with ads that promote the reasons to use a drug and the brand name and minimize risk. Her group asked CDER to rethink rules on DTC advertising, to request more resources for monitoring advertising and to place a greater emphasis on public information. If DTC advertising continues, industry should be required to fund an independent source of critique on ads. In commenting on Dr. Mitsumoto's observation, she said advisory committee members get the best advantage from consumer input if it occurs after the presentation and discussion take place.

National Council on Patient Information Education: William Ray Bullman, M.A.M., said his organization is concerned about the nature of information in DTC ads distributed at the point of prescribing and given to patients in supplemental information with their prescriptions. He encouraged CDER to conduct research on which formats improve outcomes and information exchange. The recommendations in the action plan remain untested in the real world. He called on CDER to coordinate a national Consumer Medicine Safety and Education Program that would educate consumers and health care providers about medicine information, promote question asking and information sharing, and better equip consumers and health professionals to recognize and report medication-related errors. He suggested that it be modeled on the Partnership for Food Safety funded by industry, consumer groups and federal agencies including FDA and USDA. Ideally, the program would be launched in October 1999 to correspond with the "Talk About Prescriptions" Month. Americans need such a campaign because consumers die or fail to get better because of compliance problems. He cited the example of 100,000 auto accidents and 15,000 deaths from sedative effects of drugs. The public shouldn't be placed at risk from sedated drivers. Lack of consumer awareness of the value of medicines properly used, their risks, and their potential for harm when used incorrectly are major barriers.

American Society of Health-System Pharmacists: Charles E. Myers spoke for his organization that represents 30,000 pharmacists who work in hospitals, home care, nursing homes and other institutions.

- *Drug marketing and advertising:* His group is opposed to DTC ads because they are unsure how it can be done given the nature of advertising and prescription drugs. Most information must be interpreted by learned professionals. Ads burden the health care system with partially informed patients. Ads tend to minimize risks and give more prominent attention to benefits. Given their brevity, broadcast ads are inherently misleading. The mere printing of package insert information doesn't give appropriate interpretive information. There is a real danger that self-diagnosing and asking for medicines can lead to inappropriate use. He doesn't believe advertising can ever be not misleading.
- *Information:* The FDA asserts that it is an authoritative and independent source of information; however, the FDA is the best source on approved uses. Others groups, such as his society, are independent are also good sources. Summaries for new drugs are a good step. Fax-on-demand for package inserts is needed. CDER needs a widely published number for professional and consumer information. CDER's Web site posting of drug information was questioned about whether it can be kept up-to-date. FDA has made great strides with the posting of safety notices. Automatic mailing to constituents is appreciated.
- *Post-marketing surveillance:* He called for a method of anonymous reporting. Hospitals can now report anonymously through USP. Updates on safety issues should be published periodically. Poor product design is a factor in many medication errors. He is aware of increased premarket review, but ideally retrospective review would be helpful. His group supports access to the MedWatch database by others so that additional analyses can be done.

Panel B Discussion

Dr. Temple asked if people were concerned about DTC advertising's lack of balance or if the problem was with DTC advertising itself. Ms. Pearson said that one of the premises of her group is that getting balanced information to women is a good in and of itself. However, her group is starting to doubt if even the best balanced information in advertisements can match the power of the accompanying visual images. Dr. Temple asked if she thought ads promoting health seeking behavior were OK. Ms. Pearson thinks they may be OK, but advertising is a very sophisticated way of communicating and may leave an unbalanced impression.

Ms. Baylor-Henry said she had concerns about DTC campaigns conducted prior to August 1997, which could either provide imagery without the name or the name without the indication. She asked if it was less confusing to link the name of the product to the ad or to return to pre-August 1997 days when indication and drug name were unlinked. Ms. Pearson observed that problems were less pervasive with the pre-August 1997 type of ad.

She stated that ads with name and condition create a lasting impression that isn't balanced. Mr. Myers agreed with consumer groups' criticism of DTC ads. He said that it appears to be a public service to have ads that say see your doctor for a new treatment for a certain condition. He appreciated that it will be an intensive monitoring effort for the FDA. Mr. Bullman said the genie is out of the bottle and it would be counterproductive to roll back to information-seeking spots. Ads provide a chance to educate as well as promote. Particularly in print ads, he would like to see an educational message rather than the microscopic brief summary that is currently printed.

Dr. Goldman observed that the MedWatch Web site has summaries of all safety reports but is underutilized. Mr. Myers responded that his group's Web site is underused as well. He said the Web sites need to be advertised. He said there needs to be a regularly scheduled release of alerts. There is power in scheduling. Dr. Goldman said safety alerts go out as the occasion occurs. Mr. Myers said periodic summaries are needed as well. Dr. Smith sought input on CDER's Web site especially with respect to off-label use. She didn't believe that the agency can put up information about off-label use. Mr. Bullman responded that FDAMA has a provision for patient-specific information about an off-label use at the point of dispensing. He said it is technologically challenging to keep information up-to-date on approved uses, let alone off-label ones. However, the lag time puts consumers at risk. Mr. Myers agreed that information needs to be science based. His comment on keeping the FDA Web site up-to-date was meant to address the usefulness of FDA's information after a drug has been approved for a while. Information about newly approved products is useful. He questioned how useful it would be in the long term, especially if most of the uses for the drug turned out to be off-label.

Dr. Temple observed that non-adherence problems and the sedating effects of drugs are not the things one normally thinks about. He asked how an information program could avoid promoting one drug over another when discussing non-sedating effects. Mr. Bullman said he thought there were ways to do it and avoid the promotion of a specific drug. He said a whole gamut of educational opportunities exists for drugs and foods, and for drugs and alcohol. He advocated educational programs aimed at a general set of questions about drugs that patients can pose to their doctors.

Ms. Baylor-Henry said that in the changing health care environment, FDA hears that patients have to be their own advocates. Ms. Rouleau said she makes a distinction between informing consumers on how the system works vs. advertising that encourages consumers to diagnose their own conditions and demand a specific drug. Consumers need to understand the system, she said, but it's a big jump to say there's a need to advertise drugs. She felt that ads put doctors and patients at odds. It's important for consumers to understand the side effects of drugs. She's not ready to ask consumers to be their own physicians.

Dr. Woodcock observed that many of the things they were discussing were health policy issues. The difficulty for FDA, she said, is that there is little research to support one position over the other. FDA relies on people's opinions, which creates a difficult

environment in which to make policy. Mr. Myers suggested that ACHPR and groups like the National Patient Safety Foundation might want to address these issues.

Dr. Goldman observed that postmarketing surveillance is a loop. FDA relies on partners, he said, and uses two listserves to let people know when something has been posted to the MedWatch Web site. He added that the FDA has received very positive feedback on its patient Qs and As when they are released.

Ms. Baylor-Henry noted that FDA, after two years, will reexamine the DTC ad issue and the public health impact of DTC ads.

Panel C

Patients'Coalition: Scott Sanders presented recommendations from the coalition.

- FDA needs more resources. He recommended working with stakeholders to build support for resources. Section 406 provides the mechanism to document requirements and develop a professional judgment budget, a process similar to what NIH does.
- FDA should reassert its role as a regulator. The skewed debate over the last few years has distorted FDA's role. The mission is to protect public health. FDA shouldn't compromise public health to avoid harming a particular company or type of company. The mission and roles of a regulator and the regulated industry are distinct. Evidence of skewed debates is the question asking about balance between pre- and post-market activities. The answer is to find resources to do both.
- The agency should create an office of drug safety. The current situation is alarming. CDER has 60 people to monitor 3,200 drugs. He cited the recent JAMA study that showed 106,000 Americans died and another 1.3 million were injured as a result of adverse reactions to properly prescribed drugs. This is in sharp contrast to 4,000 FAA inspectors to monitor 11 major and 70 smaller airlines. In 1996, aircraft accidents accounted for 945 deaths. The new office should have its own advisory committee and capacity to use all public health tools.
- FDA should strengthen its post-marketing research and surveillance. FDA lacks civil penalties and needs authority to compel post-approval trials. Many drugs are approved quickly on accelerated approval. Patients desperately need post-approval data. Monitoring and completion of this research must be a top priority. Status of post-approval studies must be in a public report.
- FDA also needs a fast-track withdrawal mechanism.
- Patient and consumer groups need better and easier access to FDA information.

Center for Medical Consumers: Arthur A. Levin, M.P.H., endorsed everything said by other consumer advocates. He called the Modernization Act a retreat from the agency's historic mission. He was critical of DTC advertising. He gave the example of the Rezulin

ad that downplayed liver toxicity. There are confirmed reports of 14 dead and unconfirmed reports of about a dozen more deaths. The ad prominently displays three pictures of happy people and near the bottom is a text statement of risk. The drug was withdrawn in the United Kingdom. This is a hard sell for a new drug. The ad pretends to know a lot more about the drug's risk than is actually known. Deaths due to drug reactions are the fourth or fifth leading cause of death. Prescription drugs are a public health risk. A well-informed and properly informed consumer may be the only public health protector. He discussed the history of MedGuides. Every industry group opposed them and called them overkill. Every consumer group supported them. The Keystone process was long and difficult. Every industry representative on the panel opposed independent monitoring. He called on FDA to revisit the private sector mandate in preparation for the year 2000 review. He cited examples of insufficient written information from commercial vendors. Steroid information sheets failed to contain information on gastro-intestinal toxicity. The safety net to protect from harm is badly frayed..

American Society for Clinical Pharmacology and Therapeutics: D. Craig Brater, M.D., established in 1900. More than 2,100 M.D.'s, Ph.D.'s and Pharm.D.'s engaged in research and education in research and development.

- *Safety of marketed products:* ADRs cause more than 100,000 deaths. The solution is education of public and health professionals. There is a lack of resources and a need to do research. There are substantial amounts of resources invested in premarket events. NIH has an abysmal track record of supporting patient-oriented research. There is a major problem in getting resources. The Centers for Education and Research on Therapeutics in legislation is a starting point. The problem is going to increase. He called for an increase in the drug safety staff at FDA. There should be a way to leverage the vast databases of PBMs. They have access to databases that identify concomitant drug administration. FDA should make post-marketing safety decisions independent from the medical review process to prevent any conflict of interest. He called for expanded regulatory research and more research on lifestyle altering drugs.
- *Maximum information for consumers:* A critical gap in provision of quality drug information is widening at a time when drug prescription and usage is increasing. FDA could specifically act to fill the gap left by loss of AMA drug evaluations and USP drug information resources. A frequently updated Internet database on drug label information is needed.
- *Scientific infrastructure:* Staff in the agency need to speak modern science and be able to communicate at an equal level with scientists in industry. Recruitment, mentoring, maintenance and renewal of scientific leadership is needed. Bringing in academics is one suggestion. He suggested time-limited tenure for division and office directors. Everyone in his department has an annual review. He suggested national search committees with internal and external experts. He said FDA should consider a sabbatical program. Internal FDA and contract scientific research should be augmented. Advisory committees should become more skilled and independent and

have a clinical pharmacologist on each committee as well as a biopharmaceutical scientist.

Panel C Discussion

Dr. Schwetz asked if mechanisms for FDA scientists to work more closely with industry could be reconciled with independence. Dr. Brater answered that people can keep this clear. Advances in science are so rapid that maintaining the level of scientific expertise is imperative. If that bumps up against regulatory responsibilities, wise people can figure it out. FDA requires the right expertise when it's needed. Mr. Sanders provided an example of deciding on appropriate surrogate markers. He said the various parties can have a conversation, but the ultimate decision remains with the agency.

Dr. Woodcock said that the agency has heard comments on excessive requirements and a number of panelists have said these have diminished. She said she didn't have statistics at hand, but has the impression that the size of drug development programs has grown and the quality of reviews has improved. She asked if anyone had a factual basis for asserting that standards had lowered. Dr. Brater said his bet was that the increase in size of NDAs was not driven by the regulatory environment but by the health care environment. He said drug developers have to generate data on cost effectiveness. Dr. Woodcock said that still increased safety. Dr. Brater remarked that problems arising when drug is exposed to large numbers of patients can't be solved at NDA end. Dr. Woodcock said there are rare events and use events that lead to safety issues that can't be uncovered in development. Mr. Levin commented that a lot of research says that there are preventable and nonpreventable safety issues. If the number and complexity of drugs increases, then risks increase. These issues weren't well-studied in previous decades. He asked, as a public health agency, shouldn't the FDA be looking at this. Dr. Woodcock replied that the agency agreed. Dr. Lumpkin said that much has to do with perceptions. Airplanes, for example, are items that are essentially clones and obey the laws of physics. People assume correctly that there should not be an airplane crash. There are good metrics on the risk of airplanes. It's not that easy with drugs. Drugs have known reactions, unknown reactions, inevitable risks, and preventable ones. It's a multifaceted problem. He observed that there is a lack of data on the issue. Sanders admitted his airplane analogy was not perfect, but his point was in the disparity of resources put into the problem. Dr. Brater said that both were making a plea for more research.

Ms. Gray mentioned that several panelists had characterized FDAMA as a retreat. She asked if they have the same characterization of the international harmonization effort. Dr. Brater said his group was very supportive. More uniformity, he said, would be better. That doesn't mean that there aren't a host of issues. Mr. Sanders replied that patient and consumer groups have struggled just to learn about the U.S. drug approval process and comment on those issues but he didn't have the expertise to comment on harmonization.

Dr. Lumpkin asked for clarification about a different risk-benefit for lifestyle modifying drugs. Dr. Brater mentioned Minoxidil for hair replacement versus heart disease. Dr. Lumpkin asked if Dr. Brater was advocating different safety and efficacy standards. Dr.

Brater said his comments were aimed more at the educational level than to the prescriber and consumer. Mr. Levin said one could argue for two different categories. Most drugs that come on the market are not breakthroughs, he said. A different risk-benefit ratio is important in his calculus. There's no reason to take a new drug for a condition that has adequate treatments, he said. Dr. Woodcock said that this different risk-benefit calculus is considered but not so overtly. Risks that are quite tolerable for cancer are not tolerable for OTCs or others, she said.

Mr. Ellsworth asked for suggestions about a stronger system to compel phase IV trials. Mr. Sanders replied that the first thing to do is use the public reporting requirement in FDAMA. Legislation calls for a company to say why a trial is not moving forward. Public humiliation will be tried, he said. The agency has to commit to following these drugs, he said.

Ms. Suydam said that a number of people were asking the FDA to advocate on its own behalf. She observed that there is a legal prohibition against this. Mr. Sanders said his group would suggest a "professional judgment" budget similar to the process used at NIH. He said consumer and patient groups have no idea how much money the FDA needs to do its job. Ms. Suydam said the agency views the 406 process as a way to lay out what is needed.

Dr. Lumpkin asked if user fees would be the way to go to support post-marketing surveillance or if it was a societal responsibility. Mr. Levin said that consumer advocates base their call on the FDA on the fact that it is supported by tax dollars. As user fees increase, the country runs the risk of privatizing public health. Those who pay also get the policy, he said. Private funding of a public agency is worrisome, he said, and he was shocked at how much of CDER's funding comes out of PDUFA.

Open Floor Statements

none