Getting Outside Advice for Close Calls

"Viewpoints vary between concerns of individual clinicians and what may affect the doctor-patient relationship, or how a drug affects a patient circumstance .... A professional woman on the committee, for instance, takes the position of the woman patient, asking whether medicine is doing something too intrusive, exercising too many prerogatives, or presenting an unreasonable risk for the patient."

— Ezra Davidson Jr., M.D., professor and chair, Department of Obstetrics and Gynecology, Charles R. Drew-University of Medicine and Science, Los Angeles, discussing the Food and Drug Administration's Fertility and Maternal Health Drugs Advisory Committee, which he chaired for several years.

Ezra Davidson Jr., M.D., serves on one of 18 committees that advise FDA about safety and effectiveness of drugs—particularly on decisions that are "close calls."

Of the 11 members of his committee, 10 are educators. Seven of the physicians specialize in obstetrics and gynecology—three also in reproductive biology. Two are epidemiologists (specialists in the incidence and prevalence of disease). Other areas represented are nursing and behavioral sciences. Committees meet in the Washington, D.C., area, generally at FDA headquarters in Rockville, Md., and those on Davidson's committee travel from as far away as Hawaii. The executive secretary, an FDA medical officer, connects the committee with the agency.

It may seem unnecessary for FDA to seek outside advice. After all, the agency employs its own full complement of scientific specialists. But outside experts add a wide spectrum of judgment, outlook, and state-of-the-art experience to drug issues confronting FDA. "We seek scientists with a broad range of expertise and different backgrounds," says John Treacy, director of the advisors and consultants staff in FDA's Center for Drug Evaluation and Research.

These expert advisers add to FDA's understanding, so that final agency decisions will more likely reflect a balanced evaluation. Committee recommendations are not binding on FDA, but the agency considers them carefully when deciding drug issues.

Members

Most members of FDA's drug advisory committees are physicians whose specialties involve the drugs under the purview of their committee. Others include registered nurses, statisticians, epidemiologists, and pharmacologists (who study drug effects in the body). Consumer-nominated members serve on all committees. As voting members, they must possess scientific expertise to participate fully in deliberations. They must have worked with consumer groups, so they can assess the impact of decisions on consumers. The committees range in size from 10 to 15 members, but most have 11. Each committee advises a corresponding FDA drug review group.

All government advisory committees are regulated by the Federal Advisory Committee Act of 1972, although FDA began using panels of outside experts in 1964. Each committee must be renewed by FDA every two years, or its charter automatically expires. Renewals must be approved by the Secretary of Health and Human Services and the Administrator of the General Services Administration.

The FDA Modernization Act of 1997 created a new advisory committee and added new provisions for advisory committees. The new committee is the Pharmacy Compounding Committee, which will advise FDA on a variety of pharmacy compounding issues. Among the new provisions is a requirement that the committee meet within 60 days of when a subject is ready for review and that the agency take action within 90 days of a committee recommendation or give the reason that no action has been taken. New committees are required to have both consumer and industry representatives. In addition, at least two members must be specialists or have other expertise in the particular disease for which the drug is indicated. There are also new conflict-of-interest provisions that limit voting and prohibit members from voting on their own scientific work. Finally, training is mandatory for all members prior to their first meeting.

Committee Independence

To encourage the committees' independence, FDA recruits members from a broad range of qualified candidates. Sources of nominations—with emphasis on identifying women and minority candidates, include professional, scientific and medical societies; medical and other professional schools; academia; government agen-

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cies; industry and trade associations; and consumer and patient groups. FDA's Office of Consumer Affairs, in particular, seeks suggestions for consumer-nominated representatives through agency field offices, current and former consumer-nominated representatives, and diverse consumer organizations with national and local interests and a widely varied membership, representing women, older people, African Americans, Hispanics, and Asians. Requests for candidates also appear in the *Federal Register.*

FDA staff members review the nominations (which can exceed 200 candidates) to identify the best mix of expertise for the particular committee. A list of nominees is then sent to the Office of the Commissioner for final selection. Committee chairs are also selected by the commissioner; they are not elected by the committees.

Meetings

Committees typically meet two to four times a year, but may meet as often as FDA needs them. FDA announces upcoming meetings in the *Federal Register.*

Members receive $150 a day while attending committee meetings, and reimbursement for costs of travel, food, and lodging. This attendance is a public service on the part of many members, who forgo seeing patients or conducting research or teaching activities to serve FDA. Thanks to the aptly named "Government in the Sunshine Act" of 1977, meetings of drug advisory committees are public, except when a topic's open discussion would be an invasion of privacy or when confidential, commercial, or trade secret information or law enforcement investigations are presented or discussed. Even at a closed meeting, there must be an open portion at which the public—as time allows—can give presentations, ask questions, and take part in general discussion. Most meetings are entirely open.

FDA almost always sets the agenda and prepares the questions for each meeting. Anyone, however, may ask that a specific drug issue be brought before the appropriate committee. When a committee itself asks to review a matter within its purview, this is granted whenever possible.

Types of Advice

FDA may especially want a committee's opinion about a new drug, a major new indication for an already approved drug, or a special regulatory requirement being considered, such as a boxed warning in a drug's labeling.

The committees may advise FDA on necessary labeling information and help with guidelines for developing particular kinds of drugs, such as those for anesthesia, heartbeat irregularities, and cancer.

They also may address such questions as whether a proposed study for an experimental drug should be conducted and whether the safety and effectiveness information submitted for a new drug is adequate for marketing approval.

For instance, Cognex (tacrine), the first drug approved to treat Alzheimer's disease, was the subject of several meetings of the Peripheral and Central Nervous System Drugs Advisory Committee during its clinical testing.

When the committee first met to consider Warner-Lambert Co.'s application for Cognex in March 1991, it concluded that available evidence did not support approval. On the basis of additional data submitted in July, the committee still recommended against approval, but advised that studies be conducted with a higher dose, over a longer time. The committee also recommended a Treatment IND (investigational new drug)—an FDA procedure for promising drugs for serious diseases that provides for wider use than is usual during the preapproval stage—provided no satisfactory approved treatment existed and patients wouldn't be exposed to unreasonable risk. FDA granted the Treatment IND in December 1991, after finding the drug appeared to slightly improve mental function in some patients at low doses and might be more effective at larger doses. The Treatment IND, begun in February 1992 and involving more than 7,400 patients, showed that Cognex provided a small but clinically meaningful benefit for some patients with mild-to-moderate Alzheimer's disease. Meeting again in March 1993, the committee recommended approval of the marketing application. FDA approved Cognex in September, after reviewing the additional information from studies.

During a meeting of FDA's Oncologic Drugs Advisory Committee, committee member Paul Bunn, M.D. (left), director of the University of Colorado Cancer Center, gives his opinion about a cancer drug being considered for approval. Daniel Ihde, M.D., Washington University School of Medicine, St. Louis, Mo., listens.

Below, FDA medical officer Grant Willams, M.D., tells the committee, seated at the tables, about the drug. The audience at FDA headquarters in Rockville, Md., includes drug firm representatives and consumers.

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Adverse Reactions

FDA's advisory committees may also consider reports of adverse reactions to an already marketed drug. If there are severe reactions or deaths and it's not clear what's going on, the agency might call a special meeting.

For information about FDA advisory committee meetings, call (1-800) 741-8138. In the metropolitan Washington, D.C. area, call (301) 443-0572. This information may also be obtained online by accessing the FDA Internet site on the World Wide Web at http://www.fda.gov/.

For information about how to nominate a consumer representative, write to the Office of Consumer Affairs, FDA, HFE-88, Room 16-85, 5600 Fishers Lane, Rockville, MD 20857.

Typical questions include:

- Should the dosage schedule be changed?
- Should certain groups of patients receiving the drug not be getting it?
- Should the contraindications (situations when the drug should not be used) be changed?
- Are the reactions to the drug also seen with other drugs in its class?

FDA received some 50 reports of serious reactions, including three deaths, to Omniflox (temafloxacin) in the first three months of marketing. A fluoroquinolone—one of a newer class of antinfective drugs—Omniflox had been approved in January 1992.

Side effects included dangerously low blood sugar levels in elderly patients, anemia due to excessive destruction of red blood cells, kidney failure, blood-clotting problems, and abnormal liver function. The manufacturer voluntarily withdrew the drug.

FDA then asked its Anti-infective Drugs Advisory Committee to discuss the problem and consider implications for quinolones in development.

Nonprescription Drugs

Over-the-counter drugs, too, benefit from advisory committee deliberation. From 1972 to 1981, at FDA's request, 16 special panels evaluated the effectiveness and safety of all classes of OTC drugs then on the market.

During hearings before the Advisory Review Panel on OTC Miscellaneous External Drug Products in 1980, New Jersey pharmacist Carmine Varano cited disastrous incidents involving camphorated oil: A 2-year-old died after exposure to camphorated oil on the chest for nearly 80 hours, a 15-month-old became confused and had seizures after crawling through spilled spirits of camphor, and an infant nearly died after camphor ointment was rubbed on its chest. Varano reported he had data from a Detroit hospital about 26 camphorated oil poisonings between 1975 and early 1979. FDA accepted the panel's advice to put camphorated oil in its place—off the U.S. market. Those OTC panels completed their review tasks and have been disbanded. OTC issues are now brought to the agency's Nonprescription Drugs Advisory Committee, which includes a voting consumer-nominated representative and a nonvoting industry representative. On a given issue, the committee will ordinarily meet jointly with another committee with special expertise in that issue. There have been a few instances in which FDA has *not* followed a committee's recommendations. Treacy cites the Rx-to-OTC switch of the pain reliever naproxen sodium, previously sold only by prescription under the trade name Anaprox and now also over-the-counter as Aleve. In June 1993, the combined arthritis and nonprescription committees voted 7 to 4 against the switch. "They had a lot of reasons," Treacy says. "The dose was too high. The labeling for people over 65 was incorrect because they excrete the drug at a *slower* rate. The members requested labeling for children because the drug makes the skin more photosensitive, and children already sunburn more easily than adults. Also, the members were uncomfortable with FDA's policy of allowing a manufacturer to mention in the label any of a list of several types of pain on the basis of studies of just any two types on the list. Although this policy had been suggested by an advisory panel before being accepted by the agency, members suggested that our scientific knowledge has increased to the point where we can be more specific."

The manufacturer, Syntex Laboratories, listened to all the

objections, Treacy says, and, working with FDA, immediately altered the dose interval and the dose, and changed the labeling for people over 65 and for children.

FDA had a follow-up meeting to brief the committees on the changes and its decision to approve the switch.

"The bottom line is FDA's," Treacy says. "The committees are advisory only. In approving the switch, we took into account the objections of the members. However, we treated it just like all the other OTC painkillers in terms of the labeling in order to give it parity with other OTC analgesics."

Managing Conflicts

The National Academy of Sciences' Institute of Medicine published findings in December 1992 of a study it did—at FDA's request—of the agency's advisory committees. FDA had been having increasing difficulty identifying potential members with needed expertise, but without financial or professional interests that could lead to conflicts of interest or the appearance of conflicts of interest. The institute confirmed that the system was fundamentally sound and did not need major changes. But it recommended a number of administrative and procedural changes regarding committee membership, committee operations, integrity of the committee system, and FDA organization and management of the system.

While the institute's study was going on, FDA conducted its own analysis of its advisory committee system. The outcome of the two reviews led the agency to concur with nearly all the institute's recommendations, which are reflected in how members are recruited and how meetings are managed today.

"We did a lot of work to strengthen the integrity of the system by resolving conflicts of interest up front," says John Treacy, director of the advisors and consultants staff for FDA's Center for Drug Evaluation and Research.

Throughout the government, advisory committee members are subject to federal laws and regulations prohibiting participation in any official action in which they have financial interests—which the law says include those of their regular employing organization. If a member is on the faculty of a university that has a grant from the pharmaceutical firm to study the drug to be reviewed by that committee, the member can't act on that issue, Treacy says. The law does allow waiver of the interest.

"Before every meeting," Treacy says, "we send members a questionnaire, stating the issues coming up and the companies with financial interests. We ask, 'Do you own stock or have grants or contracts involving these issues or firms?' If there is a conflict, we exclude the person, or, if our need outweighs the conflict, a waiver may be granted."

In a typical meeting with 11 members, there are usually two or three who have waivers, he says. (Sometimes there are none; other times, more than three.)

Criteria for granting a waiver are based on many factors, such as the amount of the financial interest, what percentage of a person's net worth that interest is, and the impact on the firm if a given product is approved or disapproved.

For example, a waiver would not be granted, Treacy says, if a member owned more than $100,000 in stock in a firm whose drug was coming before the committee, and this was more than 5 percent of the person's net worth.

"On the other hand," he says, "if the member's university had a grant of less than $15,000 to study a drug to be discussed, and the member was not involved with the grant, we'd generally grant the waiver."

Nevertheless, Treacy emphasizes that FDA carefully considers committee recommendations, "so we're reevaluating what is appropriate labeling for all OTC painkiller products. In fact, at another advisory committee meeting on Sept. 8 and 9, 1994, the members discussed what indications for the products must be studied." As these many examples show, recommendations from advisory committees supplement FDA expertise and add to the quality and credibility of the agency's decisions.

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Advisory committee members benefit, too. Says Fertility and Maternal Health Drugs Advisory Committee chair Davidson: "It's a great educational opportunity, whatever the issue. As an ob-gyn, academician, and otherwise inquisitive person, I find this advisory panel to be a mixture of science and policy that attracts my interest."