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Looking Through a Window of the Food and Drug Administration: FDA's Advisory Committee System

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The U.S. FDA is one of the most recognized and respected federal agencies in the world. It is responsible for food safety policy and for the regulation of more than 150,000 marketed medical products. Not only does the Agency review new investigational products, but it also continues its oversight for the entire life cycle of the product from its preclinical development phase to its continued presence in the marketplace. Given the exponential explosion of scientific discoveries over the last century, how does this relatively small government agency remain current on all emerging technologies to appropriately evaluate the cutting-edge scientific medical developments that are presented to it for approval? Within the Agency's scientific armamentarium, one of its most important resources is the FDA advisory committee system.

Extensive use of most of the federal advisory process began shortly after the Second World War when it became apparent that the use of public meetings, as functional parts of governmental agencies, improved communication and citizen acceptance of new statutes and regulations. The FDA did not initially take full advantage of the advisory committee process, because the post-war administration believed that the FDA's experts were capable of making appropriate independent regulatory decisions. However, over the decades, rapidly changing complex technology, additional legislation, and increased consumer activism have necessitated the establishment of a strong advisory committee system within the FDA. Scientific advisory committees complement the Agency's scientific expertise by bringing cutting-edge research, patient and patient caregiver concerns, and industry and consumer advocacy viewpoints to the table for discussion.

FDA OVERVIEW

The mission of the FDA is to protect the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safe, and affordable, and helping the public get the accurate, science-based information. The FDA is divided into the six Centers (Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, Center for Drug Evaluation and Research, Center for Food Safety and Applied Nutrition, Center for Veterinary Medicine, and the National Center for Toxicological Research), the Office of the Commissioner, and the Office of Regulatory Affairs (FDA's enforcement arm). Approximately 10,000 individuals work at the Agency: this includes physicians, nurses, dentists,

microbiologists, chemists, pharmacists, toxicologists, statisticians, biopharmaceutists, engineers, economists, and administrators.

The public entrusts the FDA to safeguard its health and safety by making timely and credible independent scientific decisions on products that it regulates. In the most recent past, it has been challenged by such multifaceted topics as variant Jacob-Creutzveldt disease, silicone breast implants, hormone replacement therapy, ephedra, gene therapy, vaccine efficacy, allogeneic islet cell transplantation, blood donor deferrals, and emergency contraception. Just how does the Agency fulfill its mission of answering difficult scientific questions? When a pre-market new drug application (NDA) is submitted, a team of reviewers examines "the sum of its parts." The chemist examines the sponsor's new product chemistry and manufacturing specifications, the toxicologist looks at the preclinical animal or in vitro studies, and the physician reviews the data of the pivotal clinical studies. A comprehensive discussion of the FDA review process is beyond the scope of this article, but the simplest description of the FDA review is that it is a comprehensive audit. Consider a protocol in which a determination of cure or failure requires a 1-month posttreatment clinical assessment. The sponsor determines that the cure rate or efficacy is 88% or that eight of nine (8/9) persons were cured, one person failed treatment (1/9), and one patient was not evaluated because he did not return for the 1-month posttreatment evaluation. If the clinical reviewer determines that the reason for the lack of follow-up was due to disease progression, the FDA will reassess the cure rate as 80% or eight (8/10) cures and two (2/10) failures. Different judgments may become topics of discussion at an advisory committee meeting.

THE WINDOWS

The advisory committees' role is to offer the FDA the very best advice possible on related questions posed by the Agency on a product of regulated industry. It is important to understand that the committee's function is *to give advice*; however, the Agency is *not bound* to follow that advice.

The FDA's advisory committees lend credibility to the FDA decision-making processes by having public discussions of controversial topics by the world's experts, the Agency staff, and the Agency's stakeholders (industry and consumers). Every meeting also serves to keep consumers abreast of the latest developments in the industry as well as affords them the opportunity to comment in an open public hearing session.

The FDA has 30 advisory committees, 18 device panels, 8 chartered subcommittees, and 1 committee that it administers on behalf of the Office of the Secretary, Department of Health and Human Services (DHHS). The committees are divided along product lines (e.g., food, devices, drugs, and biologics) and body systems (e.g., cardiovascular or gastrointestinal products). Committees are either mandated by legislation (five) or established at the discretion of the Department of Health and Human Services. Each committee, save two statutory committees, is chartered for 2 years. If, at the end of 2 years, the Agency or the DHHS determines that an advisory committee no longer serves a useful purpose or that it might be better incorporated in another committee's mission, it is terminated. A regular review is necessary because committee meeting costs are high. In the fiscal year 2003, the cost of the FDA's committee process conservatively cost taxpayers over $8 million for 80+ meetings.

In accordance with the Federal Advisory Committee Act of 1972 and to maximize their effectiveness, the FDA's committees are balanced both demographically and scientifically. Committees are composed of respected academicians, clinicians, consumer advocacy group representatives, industry representatives, and patients or their caregivers. Nominations for scientists originate from professional societies, industry, consumer groups, prior members, or the individual himself. In contrast to the scientific experts selected by the Commissioner of Food and Drugs or his designee, peers select their own stakeholder (consumer and industry) representatives. Concerted efforts are made to ensure that each FDA advisory committee or panel mirrors the population of America. With appropriate representation of age, race, sex, ethnicity, geographic, and other factors, a voice is available to speak for multiple population characteristics that are impacted as a new medical product is being evaluated.

Upon selection, all members, except those representing industry, become special government employees (SGEs), subject to multiple criminal statutes including 18 U.S.C. section 208 and the Emoluments Clause of the Constitution. Members serve overlapping terms for up to 4 years and are rarely renewed to guarantee fresh points of view. A Chair facilitates the meeting and influences conversation such that a discussion neither deviates from the topic nor is monopolized by any one member. Chairpersons are generally selected from existing committee members with leadership skills after they have served at least 2 years on a committee.

FINANCIAL DISCLOSURE AND INTELLECTUAL BIAS

To be credible as well as useful, the advisory committee of a regulatory agency such as the FDA must demonstrate that its members are free of financial or intellectual biases. A financial interest is an interest imputed to a person, his spouse, minor child, or employer in which a regulatory decision can result in a potential financial gain or loss. Intellectual bias is more difficult to define. It usually means that the individual has been involved in the clinical development process of the new medical product. Before every meeting, each member must disclose information related to financial holdings and professional activities related to the product(s) or its competitor(s) that are subjects of the meeting. The difficulty the Agency faces in trying to hire SGE members to serve on an FDA advisory committee is that by definition the world's experts who are engaged in cutting-edge bench science, clinical research, and independent consulting work are the very same individuals that are sought after by regulated industry. Fortunately, there is relief from this conundrum in the statutes, particularly 18 U.S.C. section 208. Basically, if the Agency's need for a particular individual's expertise outweighs his or her potential financial conflict, the Commissioner or his designee may grant a waiver so that the individual may participate. He may fully participate or be asked to participate in a limited fashion. The decision for full or limited participation depends on the level of financial conflict. The FDA has had Nobel Prize winning faculty as members on its committees; there are few individuals who can match the level of expertise in the field of these distinguished scholars. It is in an instance such as this that a waiver might be sought. It is much more difficult to find relief for an individual's intellectual bias. In fact, the FDA Modernization Act of 1997 specifically prohibits members of biologics or drug therapeutic advisory committees from reviewing matters related to their own work. The waiver criteria document (WCD) is an algorithmic guidance that shows how FDA staff manages issues related to potential financial conflicts of interest. More can be learned about financial disclosure by reading the FDA's WCD on the web (http://www.fda.gov/oc/advisory/conflictofinterest/intro.html).

Interestingly, much criticism has been and continues to be levied against members for their inevitable financial holdings related to industry. It is of note that these matters are often trivial (i.e., less than 1% of an individual's net worth) or peripheral to an individual's departmental colleague's grant from a competitor's sponsor. Nonetheless, all interests are reviewed and evaluated by the Agency's Ethics and Integrity staff. In the year 2001, the Agency was asked by its stakeholders to provide more disclosure of the financial interests. To understand how current members would feel about revealing more information publicly, a survey was conducted of its then 400+ members. Surprisingly, the members were in favor of revealing more about their potential conflicts; the members believed that more disclosure would demonstrate to the public that their meeting recommendations were objective. As a result, the FDA established a new policy whereby information relating to the nature and magnitude of an SGE's waived potential conflict of interest for a product to be discussed is read into the public record. For more information on the disclosure guidance, consult the web at http://www.fda.gov/oc/guidance/advisorycommittee.html. The Agency aims for transparency in all its processes and the advisory committee system is one window.

PASSING THROUGH THE LOOKING-GLASS

The advisory committee system is a mechanism in which a private citizen can make a difference by his or her participation in a government process. To meet the criteria as a committee *member*, one

must be a technically qualified expert who is able to interpret the complex data presented. He is either an academician and/or a member of an advocacy group or the industry. However, every meeting has an opportunity for all citizens—a required minimum of 60 minutes for an open public hearing session—in which *any* person may make a presentation of scientific fact or personal experience. In one of our most recent controversial meetings on breast implants, the FDA offered the public an 8-hour opportunity to present testimony to the committee and over 140 individuals participated.

The approval of Lotronex™ (alosetron HCl), a product for the treatment of irritable bowel syndrome (IBS), serves as an example of how the advisory committee process contributes to the FDA through the use of the advisory committee experts, the power to be heard by patient advocates and other stakeholders, and the transparency of the Agency's processes. Prior to its initial approval, several mild complications associated with alosetron HCl usage were discussed at a 1999 open public gastrointestinal advisory committee meeting. After its approval in early 2000, a second meeting was held in mid-2000 to discuss increased reports of more serious side effects. By November 2000, the FDA was seriously concerned and the sponsor voluntarily withdrew the product. Patients with severe cases of IBS appealed to the agency, because many had experienced relief without side effects. In April 2002, in a well-attended and emotional meeting of the gastrointestinal and drug safety and risk management advisory committees, the committees recommended that the risk/benefit ratio supported a restricted marketing of Lotronex for the treatment of women with severe, diarrhea-predominant IBS who fail to respond to conventional IBS therapy. The FDA followed the committees' recommendation and approved a supplemental NDA. This story illustrates the power of the advisory committees and how the Agency utilizes the open, integrative process and its participants to make its regulatory decisions.

BEING PART OF THE PROCESS

The FDA highly values the service of its advisory committee members and the relationship the process affords with consumers and industry. The system allows for full participation and empowers the FDA's stakeholders to assist in the regulatory decision-making process. For more information on the FDA's advisory committees or how to participate, consult the FDA web site at http://www.fda.gov/oc/advisory/default.htm or contact the Advisory Committee Oversight and Management Staff at 301-827-1220.

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