FDA Advisory Committees: What is their purpose, how they work and how you can become a member?

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Introduction

Advisory committees play an important role in the interactions that occur between the Food and Drug Administration (FDA) and the medical device/pharmaceutical industry. Advisory committee actions can significantly affect how we practice medicine and the advice that we give to our patients. Recently, many of us followed the FDA advisory committee discussions on the COX-2 inhibitors and the committee's recommendations. We may have altered our treatment plans for some of our patients or discussed the outcome of those meetings with our patients. You may have patients who heard about these well-publicized advisory committee proceedings, and then asked you for an explanation as to who are these committees and how do they work with the FDA. This article will help you answer these questions by providing a brief history of the use of advisory committees by the FDA, and how they have evolved to their present function. We highlight the role of advisory committees in the drug approval process and provide an overview of the key parts of the process where an advisory committee participates. Finally and most importantly, the article outlines how each member of the ACG can potentially participate as an advisory committee member whether as a physician, patient, consumer or scientist. We encourage our membership to consider serving the public's interest by serving on an FDA Advisory Committee and utilize their expertise to advise the FDA if a proposed drug has been demonstrated to be safe and effective, and should be recommended for marketing to the US population.

The FDA is one of the most recognized and respected government agencies in the world. The FDA's mission is to protect the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our 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, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health. This agency is responsible for the food safety and over 100,000 marketed medical products in the US that comprise nearly 25% of the US gross domestic product. The FDA oversees food, drugs and devices that each of us use every single day in our personal and professional lives. While most of us are aware that the FDA is responsible for the approval of new drugs and devices but the FDA is also responsible for overseeing the pre-market development phase of these products as well as the marketing phase of these products. It is critical to note that the FDA continues to evaluate these products while they are marketed in the US to ensure their safety and continued efficacy. The public trusts the FDA to safeguard its health by making credible independent scientific based decisions on the products that it regulates. To carry out this mission, the FDA employs over 10,000 physicians, nurses, epidemiologists, chemists, toxicologists,

statisticians, microbiologists, veterinarians, radiologists, engineers and pharmacists divided into six centers (groups) including Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), Center for Drug Evaluation and Research (CDER), Center for Food Safety and Applied Nutrition (CFSAN), Center for Veterinary Medicine (CVM), National Center Toxicological Research (NCTR). Each center has a specific focus and mission, e.g. CDER focuses specifically on drug products. Each Center is further divided into various departments, and in the case of CDER is divided into therapeutic areas, e.g., Gastrointestinal Products.

To accomplish this huge mission while ensuring that the highest scientific standards and expertise are being utilized, how does the FDA manage? When one further contemplates the continued logarithmic increase in scientific information and discoveries, how does the FDA ensure the best science is being utilized during their evaluation of medical products? To provide this scientific expertise, the FDA utilizes the FDA Advisory committee system that consists of several thousand experts that advise the FDA on critical scientific issues. The advisory committee's role is to offer the FDA advice on specific scientific questions raised by the FDA on a regulated product. Please note that the FDA is not bound to follow the advice given by the advisory committee and all decisions regarding a medical product reside with the FDA. The advisory committee provides the FDA with public discussions of difficult topics between the world's experts, FDA staff, industry, consumers and patients. Each advisory committee meeting also serves to keep consumers informed of the latest developments in the industries the FDA oversees as well as provide the public with an opportunity to comment on those products. The FDA currently has some 30 advisory committees and 18 device panels. The committees are generally aligned with the FDA's product lines, i.e., food, drugs, devices and biologics. Each committee is chartered for 2 years and at the end of the term, the FDA determines if the advisory committee should be continued. This ongoing review is critical due to the high cost to the taxpayers of maintaining such an advisory committee.

History of the use of Advisory Committees by the FDA

The FDA first used advisory committees following the enactment of the 1962 Kefauver-Harris Drug Amendment. These 1962 amendments now required that all drugs approved by the FDA since 1938 also have adequate data to demonstrate that the drug is effective in the disease or condition. The 1962 amendment in conjunction with the previous 1938 Food, Drug and Cosmetic Act that required safety data for each product, now required the FDA to ensure that all drug products were both effective and safe before being given approval to market the product in the US. The 1962 amendment was also retroactive, i.e., the FDA had to re-evaluate some 6000 products that had been approved since the 1938 law to ensure these products had evidence of efficacy. To accomplish this goal and for the first time, the FDA used outside scientific experts to provide advice on drug approvals. The FDA asked the National Academy of Sciences National Research Council to review all previously approved prescription drugs. This process became known as the Drug Efficacy Study Implementation (DESI) process with some 18 committees each assigned a particular class all of drugs. Each committee had approximately seven members from academia, clinical medicine, pharmacy, toxicology,

consumer and industry groups. In 1966, these advisory committees were dissolved as the FDA reviewed the value of the advisors and the use of agency resources but were reinstated in 1969 as the FDA continued to rely on the advisory committee experts. With all federal agencies increasing their use and reliance on advisory committees, Congress passed the Federal Advisory Committee Act of 1972. This Act formally outlined the committee structures, uses of the committees and their processes. The law established uniformity in the composition of the advisory committee and a process to review and dissolve an inactive committee. The act required a fair balance among the fields of expertise and known views of the members. Government employees were disqualified from serving as advisors but government employees would be responsible for setting meeting agendas, and managing the process to most effectively utilize the advisors resources. The 1972 Act also specified the process for establishment of advisory committees. An agency head was allowed to initiate the creation of an advisory committee but required to obtain a charter for the advisory committee from the General Services Administration. The intent was to establish an advisory committee only when their use was justified to minimize resource utilization. Each agency was required to renew their charters every two years to further ensure advisory committee were being optimally utilized. The act also required public accountability of all stages of the advisory process. The act requires that committee creation and member recruitment be posted in the federal register as well as meetings and the availability to the public of meeting transcripts. In 1979, the FDA added a new section in the Code of Federal Regulations (21 CRF 14) that specified the administrative procedures, allowable subject matter for an advisory committee and the role of the advisory committee members. This included recommending that advisory committee review the safety and efficacy of food additives, prescription drugs, OTC drugs biologics and devices. High priority was established for products where the approval was difficult, controversial within the scientific and public communities. The FDA further refined the process in the 1985 New Drug and Antibiotic regulations by advising when an advisory committee would be called to review a pending drug application and included important advances in the type of therapy, formulation or delivery, if the product posed concerning risks to patient safety or limited benefit relative to the risk, if the product has prompted scientific or public controversy or has received heightened regulatory scrutiny. The regulations also clarified that advisory committees be involved during the final phases of the drug approval process but can be involved at earlier stages. Finally, in 1997, the Food and Drug Modernization Act advised on the recruitment and training of advisory committee member, interactions between the advisory committee members, the FDA and industry. The act mandated that at least two advisory committee members have training specific to the disease or condition be discussed to ensure proper clinical knowledge is represented. In addition, each advisory committee is to contain consumer, patients and industry representatives to ensure all perspectives and the impact that the advisory committee advice represents. These provisions further ensure that fair balance is maintained as identified in earlier provisions. The Act also calls for training of advisory committee member in the advisory committee process, time restrictions on advisory committee deliberations and prompt notification of the public of the outcomes for each meeting. The 1997 Act also clearly refuses to grant any waivers to any advisory committee member to review their own work.

What is the purpose of an FDA advisory committee

The FDA advisory committee provides independent expertise and technical guidance related to the development and evaluation of the safety and efficacy of products under the jurisdiction of the FDA. They lend scientific credibility to the FDA product review process. They speed the review of products by providing a shared responsibility for the review and approval of a product. The Advisory committees provide a public forum to discuss matters of significant public interest as it related to drugs. The Advisory committees allow both the public and industry to remain informed of current trends in drug review process including FDA expectations and guidelines. The advisory committee provides an external review of FDA research of reviewed products and may advise the FDA on broad regulatory and scientific issues that are not related to a specific product. As previously noted, advisory committee recommendations are not binding to the FDA, as the FDA retains all final decision authority.

The advisory committee that many of us are familiar with is the Gastrointestinal Products Advisory Committee. This committee is one of 16 advisory committees that serve the Center of Drug Evaluation and Research. The CDER manages a total of 16 Advisory committees (see table 1). Most advisory committees provide advise to the FDA on the safety and efficacy of product specific for that therapeutic area. The remaining committees advise on regulatory guidelines and issues concerned with drug manufacturing.

Table 1 Listing of Current CDER Advisory Committees
Anesthetic and Life Support Drugs Advisory Committee
Anti-Infective Drugs Advisory Committee
Antiviral Drugs Advisory Committee
Arthritis Advisory Committee
Cardiovascular and Renal Drugs Advisory Committee
Dermatologic and Ophthalmic Drugs Advisory Committee
Drug Safety and Risk Management Advisory Committee
Endocrinologic and Metabolic Drugs Advisory Committee
Gastrointestinal Drugs Advisory Committee
Nonprescription Drugs Advisory Committee
Oncologic Drugs Advisory Committee
Peripheral and Central Nervous System Drugs Advisory Committee
Pharmaceutical Science, Advisory Committee for
Psychopharmacologic Drugs Advisory Committee
Pulmonary-Allergy Drugs Advisory Committee
Reproductive Health Drugs, Advisory Committee for

Who are the members of an FDA advisory committee?
Members of an advisory committee typically include academicians, clinicians, consumers, patients and industry representatives. With the exception of the industry representatives, all members are special government employees (SGE) and are subject to

the same statutes a government employee regarding their conduct and behavior during advisory committee meetings. Members serve four-year terms and are often not renewed to assure new ideas for the committee. Each advisory committee has an assigned chairman that is usually chosen from the advisory committee member after having served at least two years and having demonstrated leadership abilities. In addition to standard members, the advisory committee may also include temporary voting members as consultants or guests who may provide the necessary expertise for a specific meeting/issue. Membership is balanced in terms of their points of view. At least two members are experts in the field under review. Membership is balanced with regard to geographic area, race and gender and members are selected without discrimination on sexual orientation, HIV status, and culture, religious, socioeconomic or physical status.

Medical and Scientific Members

The medical and scientific members of an advisory committee must possess expertise relevant to the area and have a good reputation with known leadership qualities. These individuals must be acknowledged experts in their field with strong credibility. In addition, they will have demonstrated skills in the evaluation of data and have strong communication skills to facilitate committee operations.

Consumer Representative

Each advisory committee will have one consumer representative to offer the consumer's perspective to the relevant issue and the impact that an advisory committee decision may have on the consumer. They serve as liaison between the committee, interested consumers and consumer organizations. This representative must be capable of analyzing scientific data and understanding the drug evaluation process and possess strong communications skills.

Patient Representative

Each advisory committee usually has one patient's representative who may have personal experience with the disease being discussed but must be knowledgeable about the illness and the potential impact on the patients. This person represents the patient's interests to the advisory committee.

Industry Representative

Each advisory committee has one industry representative to reflect the views of the overall industry and not their own company's position to the advisory committee. The industry representative must understand how the advisory committee's decisions may affect their industry and any precedent's the committee may set.

How does an FDA Advisory Committee work?

Premeeting Work

The FDA establishes the schedules for advisory committee meetings on an annual basis, usually from October through September of the next year to be consistent with the Federal Government's fiscal calendar year. The schedule for each advisory committee is posted well in advance on the FDA's website. Typically, a committee will meet several times per year for two consecutive days. Generally meetings will be held in the Washington, DC area, usually at a nearby hotel. The advisory committee members stay at the designated hotel and are reimbursed by the government for travel expenses as well as a modest fee for each day of service. An FDA official will serve as the executive secretary for the committee to arrange for transportation lodging and set the agenda.

The agenda for a meeting may be set months in advance and is publicly disclosed in the Federal Register at least two week in advance of the meeting. The FDA may also call for an unscheduled meeting of a specific advisory committee if there are extenuating circumstances that require such a meeting.

Four to six weeks before each advisory committee meeting, members' will receive a copy of the industry product sponsor's briefing book. The industry sponsor's briefing book presents the companies best argument as to why the advisory committee should recommend the product's approval. The briefing book is usually a concise summary of the product application and clearly articulates the need for the product, the disease that it treats, and the efficacy of the product for that disease and the safety profile of the product in the intended patient population as well as normal volunteers. Most importantly, the briefing book will summarize the benefit to risk evaluation for the product. Typically, the books will be between 50 and 200 pages.

The advisory committee members will also receive in advance of each meeting an evaluation of the product prepared by the FDA staff. Included in the FDA's evaluation will be both a clinical review, statistical review and, as needed, a review of the chemistry and manufacturing of the product. This summary will indicate the FDA's view of the product and highlights the key issues that the FDA wishes the advisory committee to consider during the upcoming meeting.

Finally and most importantly, advisory committee members will receive a series of questions that the FDA wishes the advisory committee to debate and answer during the advisory committee meeting.

The advisory committee briefing materials from both the FDA and the industry sponsor are made available to the public on the FDA website 24 hours before the meeting which is consistent with the FDA's public disclosure policy.

Advisory committee meeting process

The advisory committee meeting generally follows a standard agenda. The meeting will start with the Executive secretary (who is an FDA employee) who will disclose any conflicts of interest that may exist for participating advisory committee members. The

chairman of the committee will then take over the meeting and direct the agenda. Typically, the formal part of the meeting consists of a presentation by the industry sponsor of the efficacy and safety data supporting the application to market the product, and usually ends with a presentation of the benefit-to-risk evaluation for the product. Following the industry sponsor's presentation, the FDA staff will present their views on the safety, efficacy and compare the benefits to the risks of the product. Once both of the formal presentations are complete, the chairman will typically ask for any comments from the public. The FDA would like to be notified in advance if a citizen is interested is speaking during the public portion of the meeting, but citizens who appear at the meeting are usually given a limited amount of time to address the advisory committee members. Citizens are usually asked to identify themselves and disclose any financial interest or ties that they may have to the industry sponsor. Citizens who typically speak to the advisory committee may be clinicians who have used this drug and support either its approval or non-approval. Other citizen speakers may include patients who represent advocacy groups and wish to convey to the committee their position on the product.

Upon completion of the public portion of the advisory committee meeting, the next section of the meeting begins with the discussion of the FDA's highlighted issues. The discussions focus on the questions that the FDA requested the advisory committee discuss. The questions generally represent key issues that must be addressed to enable the approval of the product. During the committee discussion, the industry sponsor may or may not have the opportunity to answer questions or provide input to the discussions. Typically, the discussion will include the advisory committee members, asking both the industry sponsor and the FDA for clarification or additional data that may answer their specific questions. The end of the meeting is focused on answering all of the FDA questions and includes a committee vote. Most advisory committee meetings will discuss questions that relate to the market approvability of the product, has sufficient efficacy data been generated, has sufficient safety data been generated and does the advisory committee feel the industry sponsor must provide additional information in the form of a post approval commitments to address the advisory committee's concerns. During the voting process, the FDA staff may ask an advisory committee member for a rationale to support their vote to fully understand the expert's thought process in analyzing the data.

How you can become a member of an FDA Advisory Committee?

Each FDA center is responsible for recruiting advisory committee members for it's respective advisory committees. The FDA publishes at least once per year in the Federal Register a call for nominations for current or upcoming vacancies on the advisory committees. In addition, the FDA website also identifies any openings for consumer, patients and industry representatives. The responsible FDA division, e.g. Gastrointestinal Products may also seek prospective candidates from previous advisory committee members, FDA staff, professional societies, academic institutions, consumer groups, patient advocacy groups, industry and self-nominations.

Upon notification of a potential advisory committee representative, the FDA Division employs a careful screening process for advisory committee members. The screening

process involves a careful assessment of the candidate's expertise on the particular subject matter and evaluates the candidate's reputation and leadership qualities. In addition, the screening process will evaluate if the potential candidate is an acknowledged expert in the field, has demonstrated the ability to analyze data and possess competent communication skills to enable satisfactory participation in advisory committee meeting process. The screening process also includes external documentation of the candidate's credentials. Qualified candidates are sent by the FDA Division Director through various levels of FDA approval and eventually are forwarded to the FDA Commissioner for final approval. The Commissioner's office will again review the application and approve the advisory committee representatives based on the need for expertise in that area, qualifications, potential conflicts of interest, and the need for fair balance.

For ACG members who are interested in potentially participating in an FDA advisory committee, they should send a copy of their CV to the chairman of this committee for consideration at the following address. The chairman will forward the CV to the appropriate FDA official for further consideration in the advisory committee representative selection process.

Send a copy of the CV to the following address.

Charles Brady, M.D., FACG
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