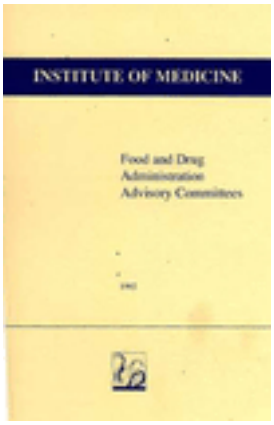

Food and Drug Administration Advisory Committees

Richard A. Rettig, Laurence E. Earley, and Richard A. Merrill, Editors; Committee to Study the Use of Advisory Committees, Institute of Medicine

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Committee To Study the Use of Advisory Committees by the Food and Drug Administration

Richard A. Rettig, Laurence E. Earley, and Richard A. Merrill, Editors

Division of Health Care Policy
Institute of Medicine

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held at the Staatlichemuseen in Berlin.

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Committee to Study the Use of Advisory Committees by the Food and Drug Administration

LAURENCE E. EARLEY,* *Chair*, Francis C. Wood Professor of Medicine, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

ROBERT S. ADLER, Associate Professor of Legal Studies, Graduate School of Business Administration, University of North Carolina, Chapel Hill, North Carolina

RICHARD A. BERMAN,* President, Howe Lewis International, New York, New York

RICHARD E. CLARK, Professor of Surgery, Allegheny General Hospital, Pittsburgh, Pennsylvania

DEBORAH COTTON, Harvard University School of Public Health, Boston, Massachusetts

J. RICHARD CROUT, President, Boehringer Mannheim Pharmaceuticals, Rockville, Maryland

CAROLYNE K. DAVIS,* National and International Health Care Advisor, Ernst & Young, Washington, D.C.

JORDAN U. GUTTERMAN, Professor and Chairman, Department of Clinical Immunology and Biological Therapy, M.D. Anderson Cancer Center, Houston, Texas

SHEILA JASANOFF, Professor and Chair, Department of Science and Technology Studies, Cornell University, Ithaca, New York

PAUL MEIER,* Professor of Statistics, University of Chicago, Chicago, Illinois

THOMAS C. MERIGAN, JR.,* Becker Professor of Medicine and Head, Division of Infectious Disease, Stanford University School of Medicine, Stanford, California

RICHARD A. MERRILL,* Daniel Caplin Professor of Law, University of Virginia School of Law, Charlottesville, Virginia

HARRY M. MEYER, JR., President, Medical Research Division, American Cyanamid Company, Pearl River, New York

FRANK E. SAMUEL, JR., Government Strategy Associates, Washington, D.C.

LOUIS E. UNDERWOOD, Professor of Pediatrics, University of North Carolina, Chapel Hill, North Carolina

ALBERT P. WILLIAMS, The RAND Corporation, Santa Monica, California
JAMES B. WYNGAARDEN,* Associate Vice Chancellor for Health Affairs, Duke University, and Foreign Secretary, National Academy of Sciences and Institute of Medicine, Washington, D.C.

Study Staff

RICHARD A. RETTIG, Study Director
STANLEY W. AMMONS, JR. Program Officer
HOLLY DAWKINS, Research Assistant
THELMA L. COX, Project Assistant
NANCY DIENER, Financial Associate
RUTH ELLEN BULGER, Director, Division of Health Sciences Policy

* Member, Institute of Medicine

Preface

The departments and agencies of the federal government, especially those deeply engaged in scientific and technological matters, have made extensive use of external advisory committees as a means to acquire independent scientific and technical advice. This use of advisory committees has received attention over time from a number of sources, including the Congress, and in recent years has been the subject of more general analytic treatment.[1,2]

The Food and Drug Administration (FDA) of the Department of Health and Human Services makes extensive use of technical advisory committees. It does so primarily in the support of its evaluation and regulation of drugs, biologics, and medical devices for human use. In 1991, prompted by the Commissioner of Food and Drugs, Dr. David A. Kessler, the FDA requested that the Institute of Medicine (IOM) examine the optimal use of FDA's advisory committees in product evaluation and in relation to agency management and agency accountability. This report results from the deliberations of a committee convened by the IOM to conduct this study.

In general, advisory committees are the major way by which the FDA obtains independent technical and scientific advice, although workshops, symposia, consultants, and extensive, often informal, contacts between agency professionals and the scientific and medical communities are other important means for doing so. Although this report focuses on advisory committees, the IOM committee recognizes and endorses the use of these other means of obtaining independent expert advice.

The FDA advisory committee system was established at the agency's initiative to provide it with technical assistance related to the development and evaluation of drugs, biologics, and medical devices, to lend credibility to its decisions and decision-making processes, and to provide a forum for public discussion of certain controversial issues.

The IOM committee believes that the primary role of FDA technical advisory committees is and should be to provide independent expert

scientific advice to the agency. It also believes that the existing FDA advisory committee system is fundamentally sound, has served the agency well, and does not need wholesale reorganization. It should be retained and strengthened. However, the IOM committee recommends a number of administrative and procedural changes that are designed to improve the performance and usefulness of the advisory committee system, to strengthen its management, and to increase its accountability.

In response to the agency's request, the report seeks to provide FDA with operational guidance on the use of its advisory committees. In doing so, it examines and makes recommendations on the recruitment and acquisition of committee membership, the agency's management of the financial conflict of interest and intellectual bias of committee members, and the operations and management of the advisory committee system.

The control of financial conflict of interest received more of the IOM committee's attention than any other topic. This priority, which was the foremost concern of the Commissioner, stemmed in large measure from the fact that the rapid change in the criteria and procedures by which conflict of interest controls were administered appeared to be impairing the FDA's ability to use advisory committees.

The issues of financial conflict of interest and of intellectual bias are great concern to the scientific community at the present time. They pervade many realms of science and medicine and have highly complex manifestations in specific institutional contexts. The IOM committee considered these issues, however, in relation to FDA's regulatory responsibilities for the evaluation of drugs, biologics, and medical devices. Consequently, this report gives great weight to the legal and administrative aspects of these matters, as these were the immediate source of FDA's problems. Although the report acknowledges the importance of broader concerns for conflict of interest and intellectual bias, it does not examine them at any length.

The IOM committee found great variation in the way advisory committees were used by the three centers responsible for drugs, biologics, and medical devices—the Centers for Drug Evaluation and Research, Biologic Evaluation and Research, and Devices and Radiological Health. One theme that runs throughout this report, therefore, calls for the development of uniform guidelines applicable to advisory committees across the three centers and for the elimination of unnecessary differences.

Another theme embedded in the IOM committee's recommendations is the need for FDA to ensure the independence of its advisory committees. In the highly-charged environment surrounding product evaluation by the FDA, charges that it seeks to influence the outcome of committee deliberations may or may not have merit but are often made by interested parties. As a result, ascertaining the validity of such charges can be very difficult.

appear to be, able to provide independent expert advice, and point to the uniform policies and procedures needed to ensure committee independence.

Finally, the committee focuses on a number of steps that the FDA should take to strengthen its management of the advisory committee system, from the Office of the Commissioner to the professionals who staff advisory committee operations. The IOM committees recommendations in this area strike a balance between those who urge a high degree of centralization of committee management in the Office of the Commissioner and those who argue that no change is warranted.

In sum, the IOM committee has attempted in this report to provide the agency with the guidance it sought in order to enhance the use of advisory committees in the evaluation of drugs, biologics, and medical devices, to improve the agency's management of the advisory committee system, and to increase the accountability of that system to the general public.

NOTES

1. Sheila Jasanoff, *The Fifth Branch. Science Advisers as Policymakers* (Cambridge, Mass., Harvard University Press, 1990).

2. Bruce L. R. Smith, *The Advisers: Scientist in the Policy Process* (Washington, D.C., The Brookings Institution, 1992).

Acknowledgments

This report results from the deliberations of the Institute of Medicine Committee to Study the Use of Advisory Committees by the Food and Drug Administration. The recommendations of the report reflect the judgments of the committee.

The actual preparation of the report under the direction of the committee has been accomplished by the collective efforts of committee members, project staff, and other contributors. The committee gratefully acknowledges these contributions.

The committee thanks the authors of the background papers that it commissioned, which provided valuable input to its deliberations. These authors include: Wendy E. Anderson, Scott Davidson, Laurie M.C. Faro, Gokuraju K. Raju, and Paul K. Stockman. Rebecca Wallace was a consultant to the project and prepared the analysis on which Appendix A was based.

The committee expresses its appreciation to the Industry Liaison Panel that it convened to advise it, especially to Marion J. Finkel, its chair. The other members were: N. Kirby Alton, Scott A. Hensley, Bruce Merchant, George Ohye, Martin Rose, Eve Ross, and R. William Soller.

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In her capacity as Director of the Division of Health Sciences Policy, Ruth Ellen Bulger provided valuable guidance over the duration of the project. Stanley W. Ammons and Holly Dawkins provided able support as members of the project staff. Thelma Cox, project assistant, saw the study through from start to finish with unflappable grace.

Contents

List of Abbreviations

CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice(s)
DHHS	Department of Health and Human Services
FACA	Federal Advisory Committee Act
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FR	Federal Register
FOIA	Freedom of Information Act
GAO	General Accounting Office
GSA	General Services Administration
IDE	Investigational Device Exemption
IND	Investigational New Drug
NDA	New Drug Application
NIH	National Institutes of Health
OGC	Office of the General Counsel
OGE	Office of Government Ethics
OSCE	Office of the Special Counsel for Ethics, DHHS
PHS	Public Health Service
PMA	Premarket Approval (application)
SGE	Special Government Employees
SMDA	Safe Medical Devices Act (of 1990)
USP	United States Pharmacopeia

Summary

The Food and Drug Administration (FDA), in mid-1992, had 41 standing technical advisory committees or panels that supported the work of its three centers responsible for the evaluation and regulation of human drugs, biologics, and medical devices. We refer in this report to these committees and their administrative support as the FDA's "advisory committee system."

In late 1991, the Institute of Medicine (IOM), in response to a request from the FDA, undertook a study of the agency's advisory committee system. This request was initiated by Commissioner David A. Kessler. He asked that the IOM examine the optimal use of FDA advisory committees in the evaluation of drugs, biologics, and medical devices and also consider such committees in relation to agency management and agency accountability. The Commissioner himself emphasized his desire to receive a report that provided operational guidance for the agency. In addition, he singled out as the most important issue the committee's examination of financial "conflict of interest" controls as they affected advisory committees.

The IOM convened a committee to conduct this study. Its members brought expertise in medical research; development of drugs, biologics, and medical devices; design and conduct of clinical trials; medicine, surgery, and nursing; regulation of drugs, biologics, devices, consumer products, and health care services; administration of medical research, health care financing, and the delivery of health care services; and health and science policy research. Three members of the IOM committee currently serve on FDA advisory committees, others have served in the past, and several were previously involved as FDA officials in the design of the current system.

In general, advisory committees are the major way by which the FDA obtains independent technical and scientific advice. Other means for obtaining such advice include workshops, symposia, consultants, and extensive, often informal, contacts between agency professionals and the scientific and medical communities. Although this report focuses on advisory

committees, the IOM committee recognizes and endorses the use of these other means of obtaining independent expert advice.

The FDA advisory committee system was established at the agency's initiative to provide it with technical assistance related to the development and evaluation of drugs, biologics, and medical devices, to lend credibility to its decisions and decision-making processes, and to provide a forum for public discussion of certain controversial issues. In general, the IOM committee believes that the existing system is fundamentally sound, has served the agency well, and does not need wholesale reorganization. It should be retained and strengthened. However, the IOM committee recommends a number of administrative and procedural changes that are designed to improve the performance and usefulness of the advisory committee system.

The Roles of FDA Advisory Committees

The IOM committee believes that the primary role of FDA technical advisory committees is and should be to provide independent expert scientific advice to the agency in its evaluation of specific drugs, biologics, or medical devices at any stage of consideration by the agency. A related role is to advise the agency on general criteria for evaluation and on broad regulatory issues that are not related to a specific product. (A role specific to CBER, which the IOM committee recognizes, is the review of intramural research programs and personnel.) Several key terms and assumptions warrant further comment.

First, "independence" refers to freedom from influence by the sponsor of the product under consideration, by any other entities or persons that could gain or lose as a result of the outcome of the process, and by the FDA itself. As a practical matter, the issue of independence of advisory committees is usually raised with respect to their relation to the FDA.

The high stakes associated with FDA decisions mean that parties disappointed by its actions have strong incentives to charge that the independence of advisory committees is compromised by undue FDA influence. However, the issues of independence and undue influence may arise as a result of subtle facets of the process; for example, the recruitment of committee members; delays in distribution of advance materials; the content and tone of agenda questions; and even seating arrangements at committee meetings. The IOM committee makes recommendations on all these issues, which collectively point to greater safeguards of the independence of committees.

Second, "expert scientific advice" implies that members will be acknowledged experts in some area of science that is relevant to the purview of the specific advisory committee.

Third, advisory committees *advise* the FDA and do not themselves have authority to make decisions that obligate the agency or any private party to a course of action.

Fourth, advisory committees respond to specific questions that have been identified by the professional staff of the agency. These questions may deal with study design or methodology, adequacy of data, and assessment and interpretation of risks and effectiveness.

Finally, although advisory committees have a prominent role in the product approval stage, they are sometimes used earlier in the product development cycle and sometimes invited to consider postmarketing issues. The IOM committee believes that it is proper for the FDA to use committees at any stage of review when scientific advice is needed, whether or not regulatory action on a specific product is under consideration.

Practical Limits on Advisory Committees

It is important to acknowledge that there are significant practical limits on the FDA's use of advisory committees. The most important limit is the time committee members are able to commit to the activity. Another limitation is the necessity that the agency be selective in choosing questions for committees from an enormous amount of material and wide range of issues under review. Still another limit is the difficulty of exercising tight control over agenda time, with the consequence that committee discussion time is often severely truncated. Finally, the use of advisory committees is limited by the resources that the FDA has available to support them.

COMMITTEE MEMBERSHIP

Nomination Criteria

The ability of the FDA to attract and retain qualified individuals who possess "expertise in the subject matter with which the [advisory] committee is concerned" is critical to the successful operation of the advisory committee system. The "subject matter" of advisory committees pertains to (a) the evaluation of drugs, biologics, and medical devices regarding their safety and effectiveness, including indications and contraindications for use and related issues of labeling, and (b) to broader technical issues related to product evaluation, such as specific methodologies for assessing a particular class of therapeutic agents. Given the purposes of FDA advisory committees,

The IOM committee strongly endorses the criterion of scientific or technical competence as a requirement for selecting all voting members of FDA technical advisory committees.

In this context, "diversity" goals of gender, race and ethnicity, and geography also guide the selection of committee members. The IOM committee believes that these goals are not incompatible with the criterion of scientific and technical competence but reflect legitimate policy objectives of a pluralistic society that are designed to ensure a range of viewpoints on what are seldom purely technical issues. However, meeting these diversity goals may necessitate special efforts by the FDA to identify women and minority group members who possess the necessary expertise.

The IOM committee recommends that the FDA continue its policy of actively seeking qualified women and members of minority groups as potential candidates for advisory committee membership.

Some constraints may limit the access of the Department of Health and Human Services (DHHS) to scientific and technical expertise as it seeks to meet its diversity goals. Current policy of the Department of Health and Human Services prevents an individual from serving concurrently on more than one Public Health Service advisory committee without a special departmental waiver. This policy limits the expertise that can be tapped for a particular committee and impedes meeting diversity objectives.

The IOM committee recommends that the Department of Health and Human Services eliminate its policy prohibiting dual committee membership and that qualified candidates for FDA advisory committees be allowed to decide whether they wish to serve on more than one Public Health Service committee. However, it also recommends that the Department exhaust other means of recruitment before it resorts to selecting individuals who serve on other advisory committees.

Although the Federal Advisory Committee Act (FACA) requires that advisory committee membership be "fairly balanced in ... the points of view represented and the functions to be performed," this criterion provides little operational guidance to agency heads in the nomination and selection of technical advisory committee members who advise on a wide and unpredictable range of issues. The IOM committee believes that "balance" for the FDA's technical advisory committees should be interpreted as a mix of relevant scientific disciplines and a diversity of scientific views. The IOM committee also believes, and court decisions now support, that it is

ultimately the Commissioner's responsibility to see that such balance is achieved.

The IOM committee considered the wisdom of recommending that 'balance" be interpreted as committee membership that included representatives (or advocates) of specific constituencies, irrespective of scientific competence. The committee rejected this premise on the grounds that the primary role of advisory committees is to provide the agency with the best scientific interpretations and advice and not to represent specific constituencies.*

Recruitment Procedures

The FDA uses a number of procedures to generate nominees for advisory committees. The only agency-wide formal mechanism is the annual *Federal Register* announcement of advisory committee vacancies required by the FACA. Informal nomination-seeking practices vary across centers, within centers, and over time.

The IOM committee recommends that the FDA adopt an agency-wide recruitment policy and develop a more systematic approach to seeking nominations on a continuing basis for potential advisory committee membership. The agency should actively seek nominees from many sources—academic medicine, professional societies, other government agencies, industry, and consumer and patient organizations. It should not rely solely on its own staff for such nominations. Each center should develop and periodically update a pool of qualified candidates, rather than simply seek nominations to fill vacancies.

The IOM committee considers the responsibility of nominating qualified individuals for FDA advisory committees to be shared by medical and scientific societies, medical school deans and department chairs, consumer and patient organizations, and other interested parties.

The IOM committee, addressing itself to these groups, urges them to accept as a continuing obligation the identification and nomination of individuals to the pool of potential FDA advisory committee members.

* The IOM committee recognized the importance of input to advisory committee deliberations from non-scientific sources such as patients, industry, and consumer groups and concluded that such input can be best achieved by testimony that relates directly to the specific agenda of a committee.

Consumer Members

The IOM committee regards the expression of consumer views on FDA technical advisory committees as both valuable and necessary. For medical device advisory panels, these views are provided by nonvoting consumer representatives, as required by statute. For all drug and two biologics advisory committees, they are supplied, not by nonvoting consumer representatives, but by consumer-nominated, technically qualified voting members.

The committee attaches great importance to the criterion of technical expertise for the nomination and selection of voting members of FDA advisory committees and opposes granting voting member status based on representation of specific constituencies. It considered and rejected the extension to drug and biologics advisory committees of the legally-required CDRH approach of nonvoting consumer and industry representatives but chose not to recommend modification of the law.

The IOM committee believes that the concept of "consumer"—both for consumer-nominated members and consumer representatives—should be expanded to include patients or patient-nominated individuals, whose viewpoints can be valuable in the product evaluation process. The FDA should actively solicit nominations from consumer and patient organizations for *technically qualified* individuals to serve as voting members on all of its advisory committees. The agency should continue to solicit nominations from the consortium of consumer organizations, but it should also reach out to other interested parties. In the judgment of the IOM committee, the practice of allowing any outside organization to screen (and thus to screen out) nominees for FDA advisory committees is unsound.

The IOM committee recommends that the FDA seek technically qualified nominees from consumer organizations and other interested parties to serve as voting members on all of its technical advisory committees and panels. Appointment should require the basic qualification of scientific or technical competence. The committee also recommends that the concept of "consumer" be expanded to include patient and patient-oriented organizations. Furthermore, no private individual or organization should be given the right to screen nominations from other sources on behalf of the agency.

Appointment Authority

Until early 1991, the Secretary of Health and Human Services appointed members of FDA technical advisory committees. This sometimes resulted in

nominees who may not have been scientifically qualified or who were selected to bring a politically preferred view on scientific and regulatory matters before the FDA. Following enactment of the Food and Drug Administration Revitalization Act of 1990, the Commissioner has appointed technical advisory committee members, but he remains under an obligation to send nomination packages to the Office of the Secretary 10 days in advance of any appointment. The IOM committee believes that vesting power to appoint committee members in the Commissioner constitutes a substantial step forward in both expediting the appointment process and ensuring that such appointments are responsive to the specific scientific and technical needs of the agency.

The IOM committee commends the Office of the Secretary for its concurrence that the Revitalization Act vests formal authority to appoint advisory committee members in the Commissioner of Food and Drugs.

Administrative Responsibility for Appointments

The Commissioner, under his authority to appoint advisory committee members, should clearly indicate to all FDA staff that center directors, office and division directors, and executive secretaries share responsibility for recruiting qualified advisory committee members. Nominations should come to the Commissioner from the center directors.

The IOM committee recommends that the job descriptions of the FDA center, office, and division directors, and executive secretaries be expanded to reflect their responsibilities for recruiting, nominating, and recommending advisory committee members.

COMMITTEE INTEGRITY

The IOM committee believes that it is essential that members of FDA's advisory committee be impartial and objective and not compromised by financial conflicts of interest. It is also critical that they be free of demonstrated intellectual bias. These goals are both practical conditions for the effective performance of advisory committees and an expression of deeply held democratic values. To achieve these ends, the IOM committee has addressed the FDA's standards and procedures for controlling financial conflict of interest and intellectual bias.

At the outset of this study, Commissioner Kessler asked that the IOM committee provide the FDA with specific guidance on the handling of

potential financial conflicts of interest involving advisory committee members. Controversies over this issue were threatening the FDA's ability to use advisory committees. The study revealed that the "problem" identified by the Commissioner involved the interaction of new conflict of interest statutes and executive orders, the legal interpretation of what these laws required, their administrative implementation, and several highly visible committee meetings. Moreover, this interaction was occurring in a highly politicized environment and in a compressed period of time.

The financial conflict of interest laws that apply to full-time federal employees also apply to advisory committee members who are appointed, as those at the FDA are, as special government employees (SGEs). As applied to advisory committee members, these laws exist to ensure that their impartiality is not compromised by their personal financial interests, or those of their spouses and immediate families, or of their employers.

Advisory committee members are screened for potential conflict of interest at two different times. First, candidates for membership are evaluated at the time of nomination and, if appointed, file a statement disclosing their financial interests. This initial screen provides the basis for a set of so-called "exclusions," namely, specific companies, products, or issues that might come before a committee and that the individual may not consider.

Although this stage of review is important, by far the greater number, and more difficult, conflict of interest issues arise when a member's financial interests are found to intersect with particular meeting agenda items. For each committee meeting, the FDA reviews each committee member's interests and affiliations in relation to the agenda to determine whether a potential financial conflict or the appearance of such conflict exists. The discovery of a potential conflict disqualifies a member from participating in the particular discussion of a specific agenda item unless a waiver is granted. The law allows a waiver if (1) the member's interest is not substantial, (2) if it is too remote or inconsequential to affect his or her impartial judgment, or (3) if the member's participation is so important that it outweighs the potential conflict. Any waiver must be sought and approved before the individual member may participate in the committee's discussion of the specific matter in question.

Events in 1989 and 1991 raised questions about financial conflict of interest to a new prominence. In 1989, in the wake of several well-publicized instances of high-level government officials engaging in unlawful financial transactions for personal benefit, including the generic drug scandals that affected the FDA (although not with respect to any advisory committee), the executive branch took action. The President's Commission on Federal Ethics Law Reform recommended that standards of conduct be updated and that

the Office of Government Ethics (OGE) be given authority to issue uniform regulations for all executive branch agencies. Executive Order 12674, issued by President George Bush on April 12, 1989, revoked the decentralized regulatory scheme that had been established in 1965 and directed the OGE to develop "a single, comprehensive, and clear set of executive branch standards of conduct that shall be objective, reasonable, and enforceable" (56 FR 33778, July 23, 1991). The OGE, which had been part of the Office of Personnel Management, was established as a separate agency of the executive branch on October 1, 1989.

Congress, unwilling to cede leadership in this arena to the executive branch, enacted the Ethics Reform Act of 1989 (Public Law 101–194) on November 30, 1989. This act included a provision [Section 208(b)(3) discussed below] intended to facilitate the use of expert advisory committees by empowering agency heads to grant waivers from the law's basic prohibition when the need for an individual member outweighed any potential conflict.

Responsibility for implementing the executive order and the new statute fell primarily on the OGE and, within DHHS, on a new unit in the Office of the General Counsel. That unit, the Office of the Special Counsel for Ethics (OSCE), is responsible for DHHS-wide policies and procedures safeguarding the ethics of government employees and for coordinating departmental policy with OGE. Within the FDA, an existing unit, the Division of Ethics and Program Integrity (DEPI), retained responsibility for approving waiver requests from the centers on behalf of the Commissioner.

In 1991, several FDA advisory committees convened to review high-profile products that presented particularly controversial problems of potential conflict of interest. The topics on which the agency sought advice included the controversy over the review of THA as a drug for the treatment of Alzheimer's disease; the dispute over the possible propensity of ProZac to induce suicide in September 1991; the safety of silicone gel breast implants in November 1991 and again in February 1992; and a controversy over the use of photopheresis in the treatment of scleroderma. Although each of these committee meetings originated in unique circumstances, all drew unprecedented attention to FDA's procedures for controlling potential conflicts of interest, and they arrived at FDA's doorstep in the same period of time.

What did these cases reveal? First, the agency had been processing waivers under outdated standards that had not been updated to accord with the 1989 statute. Second, although waiver provisions are part of the federal criminal code, government lawyers were not involved in reviewing waivers. Consequently, the FDA's Chief Counsel, in the fall of 1991, assigned two lawyers to review waivers, and they began to question the agency's existing

procedures. Soon thereafter, OSCE became involved on behalf of the department and eventually replaced the agency's lawyers. Third, OSCE and the OGE introduced new and expansive waiver standards and procedures. Fourth, the units in the FDA still responsible for conflict of interest compliance continued to perform their roles without any high-level policy guidance. Fifth, both the agency's lawyers and those from OSCE, who felt compelled to change the rules to accord with the law and executive order, dealt with waiver issues on a case-by-case basis, and provided little general guidance to those administrators responsible for managing the advisory committee system. To make matters worse, all of these changes were occurring within a very short span of time.

Not surprisingly, the conflict of interest problem was far more visible inside FDA than outside. And within the agency no one fully grasped that nature of the changes that were taking place. However, to some it appeared as though conflict of interest restrictions might cause the advisory committee system to grind to a halt because new standards had not been operationally clarified and the process had been greatly complicated.

Any attempt to address the problem must deal with issues of law, of bureaucratic procedure, and of administration. The IOM committee considered reforms that would require new legislation and those that could be implemented within existing statutory authority.

Options Requiring Legislation

The IOM committee considered several options that would require new legislation. The first would substitute for the present disqualification system one that required committee members to publicly disclose all of their interests and affiliations, and then relied on public scrutiny to assess the objectivity of their advice. The IOM committee found this approach unacceptable, as it would allow participation of members with significant, direct financial interests that should be disqualifying and would undermine the appearance of objectivity.

A second option would be a system that coupled full disclosure of all interests with a general rule barring participation by members with significant financial interests. Although this proposal may contain the core of a promising reform of the system for regulating conflict of interest, the IOM committee did not explore fully its ramifications. The committee's judgment and that of many we spoke to was that a major legislative overhaul of this magnitude was simply unlikely. Given FDA's expressed needs, our charge, and our timetable, the committee turned to solutions that were feasible within the existing statutory framework. However, this approach is clearly a candidate for further study.

Options Available within Existing Authority

What can be done under existing authority? Potentially, a good deal, as the following options suggest. Although the first option below could be implemented by FDA itself, the successful implementation of the other recommendations would require the active involvement of the Commissioner and his office, the supportive collaboration of the OSCE, and at least the tolerance of the OGE.

One theoretical option for FDA would be to avoid appointing advisory committee members as special government employees, thus circumventing the restrictions of the federal conflict of interest law. This solution has the notable disadvantage of attempting to define the problem away, which is hardly a way to instill confidence in the system. Moreover, new legislation would possibly be needed to allow payment of members and sharing of trade secret information.

Second, the FDA itself could exercise greater care in the initial appointment of advisory committee members. It could demand even more information than is currently required to enable it to identify in advance potential members whose financial interests would clearly disqualify them for some committee meetings. Yet because the interpretation of a prohibited interest is already extremely broad, and potential conflict cannot be identified before meeting agendas are set, serious pursuit of this problematic approach might disqualify valuable members and produce no gain in integrity. Moreover, the conflicts of interest that might arise over the duration of a committee membership are unpredictable at the time of appointment.

Third, the FDA, working with OSCE, could formulate and codify criteria for granting 208(b)(3) waivers. The IOM committee believes that this is essential. Codification would be a lengthy process, but some mutual understanding of the grounds for justifying a waiver is badly needed. A checklist of variables must be formulated that includes: the size of the interest; the character of the interest; the likelihood than an interest will be affected by agency action based on the committee's advice; and the actual importance of the member to the committee's deliberations. Regarding the latter point, membership alone should not be taken automatically as a decisive measure of a member's importance.

Of immediate importance is the need to clarify the criteria for dealing with potential conflicts arising from institutional or employer financial interests, research grants and contracts to committee members, and member involvement with competing products and technologies. Regarding institutional financial interests, most advisory committee members are university employees; most of their employers operate medical schools,

hospitals, and hospital pharmacies. OCSE, with the FDA, should develop clear criteria for dealing with waiver requests that arise because a committee member is affiliated with an institution, some of whose financial interests flow from such subordinate entities (e.g., revenues derived from prescribing drugs). In addition, most universities hold diversified endowment funds; it is often the case that some of these funds are invested in pharmaceutical, biotechnology, or medical device securities. OCSE, with the FDA, should clarify the criteria for dealing with these "employer interests."

The IOM committee recommends that the FDA and the OSCE begin immediately the process of codifying the criteria for granting 208(b)(3) waivers, especially with respect to institutional conflicts, research grants and contracts, and competing products and technologies.

Fourth, the agency has the authority to streamline its own internal policies and procedures for deciding when to seek waivers and how to prepare their justifications. The IOM committee believes that this action is also essential. Responsibility for preparing the initial waiver request should reside with the division. The decision to request a waiver should be made by the center director. The IOM committee sees no need for review by the DEPI or by FDA's Chief Counsel, as long as OSCE has a reviewing role. Central agency review of waiver requests should be by a high-level policy official in the Office of the Commissioner.

The IOM committee recommends that FDA streamline its policies and procedures for requesting and processing waivers. This clarification should fix the primary administrative responsibility for implementing these changes at the level of the respective centers. The authority to grant waivers should be retained at level of the Commissioner (i.e, at that of the appointing authority).

Fifth, the FDA should develop and adhere to strict schedules for processing waivers. It should present waiver requests to OSCE no later than three weeks in advance of a meeting.* The Commissioner should seek agreement from the OSCE that it will review any proposed waiver within three days. The Commissioner may even wish to establish default rules that penalize centers for late submissions (e.g., the member is disqualified or the agenda item is postponed).

* The IOM committee notes that if the FDA adopts the recommendation for advance scheduling of advisory committee meetings proposed below and in Chapter 7, it may be possible to increase this period of time.

The IOM committee recommends that the FDA, with the cooperation of OSCE, adopt a policy of strict scheduling for processing waivers and that such a policy include default rules for late submissions of waivers.

Sixth, the FDA must update the training programs of its officials with responsibility for implementing conflict of interest policies involving advisory committee members. These training programs should build around the substantive and procedural changes suggested above. Participation should be required of all FDA professional staff who deal with advisory committee members.

The IOM committee recommends that the FDA develop a training program regarding conflict of interest for all of its professional staff who deal with advisory committees. This program should be based on the policy and procedural changes suggested in this report.

Seventh, the FDA must also initiate and maintain orientation programs for advisory committee members. Individual members should clearly understand the criminal laws that govern financial conflict of interest and the justifications for granting waivers. However, the IOM committee believes that guidance on conflict of interest should be linked to a broader orientation program (discussed below and at length in Chapter 8). This linkage is important because an exclusive focus on conflict of interest will necessarily emphasize the risk of *criminal* prosecution and the need for intensive inquiry into personal financial matters—an emphasis that would surely obscure the public service dimension of advisory committee membership.

The IOM committee recommends that the FDA develop an orientation program for its advisory committee members and that this program include explicit attention to conflict of interest in the context of a broader orientation to the public service aspects of advisory committee membership.

Eighth, the FDA and OSCE, on behalf of DHHS, should seek the issuance by OGE of a government-wide general 208(b)(2) waiver regulations as soon as possible. This statutory authority has yet to be exercised but is intended to remove certain conflicts from a case-by-case determination. Institutional financial interests and holdings could be dealt with by such a rule.

The IOM committee recommends that the Office of Government Ethics develop and issue a government-wide 208(b)(2) waiver rules as soon as

possible. It further recommends that the FDA provide input to the scope of these waivers rule and that the FDA and OSCE continue to impress on OGE the urgent need for such rules.

Finally, the FDA, and DHHS, should seek the revision of Executive Order 12674 requiring case-by-case consultation with OGE on all waiver requests.

The IOM committee recommends to the President that Executive Order 12674 be amended to remove from OGE the responsibility for case-by-case review of advisory committee member waiver requests. The committee recommends that such case-by-case review authority be delegated to the departments and that OGE authority be limited to government-wide oversight of agencies' policies and procedures.

The foregoing discussion has dealt with financial conflict of interest as regulated by Section 208 of Title 18 of the U.S. Code. It has not addressed the issue of intellectual bias, which refers here to the potential effect, subtle or overt, of a scientist's prior research or public statements on his or her objectivity. Advisory committee members who bring strong opinions about specific matters to their assessment of data are not necessarily and automatically biased. A judgment of bias turns on their willingness to hold their personal views in abeyance while examining the pertinent data in a careful and impartial way.

Although the legal restrictions that might govern the treatment of intellectual bias on the part of advisory committee members may be quite uncertain, the matter should nevertheless be of concern to the FDA. One reason for such concern is that a committee whose advice is not impartial defeats the purpose of seeking independent expert advice. A second is that committee members who were not open to persuasion by evidence would erode public confidence in a mechanism that FDA has devised to generate such confidence.

The IOM committee holds the view that the FDA should be sensitive to the possibility than an advisory committee member might be so committed to a point of view on a potential matter, or so publicly identified with that view, that his or her objectivity cannot be assumed. Under such circumstances, which the committee has no evidence will occur often, the FDA should exclude that member from participating in the discussions of the matter. If the determination of bias rests on publicly stated positions, full exclusion may be warranted. However, if exclusion stems from the member's prior research, especially as a principal investigator, the FDA should not be deprived of that individual's expertise. This can be solved by

inviting the person to address the committee as a witness (or as a "guest"). A sensible approach might recognize just three roles for committee members in the case of intellectual bias: (a) full voting participation; (b) full exclusion from a meeting or an agenda item; or (c) appearance as "witness" or "guest" of the agency.

Issues of intellectual bias do not involve legal questions of financial conflict of interest. Therefore, remedies should be determined by the Commissioner, on advice of the relevant center director. Any legal ramifications should be dealt with by the agency's Chief Counsel. The entire issue, clearly, is one deserving further attention by the agency.

The IOM committee recommends that the FDA develop criteria and procedures for identifying potential intellectual bias or advisory committee members and protecting the objectivity and impartiality of advisory committees. The committee recommends that the agency routinely request information about research interests and publicly stated positions on scientific issues from advisory committee members. It recognizes that the agency must rely to a large extent on committee members themselves to provide such information.

When the agency concludes that a committee member has demonstrated a lack of objectivity on a matter, the member should be excluded from participation in the committee deliberations concerning that issue. If information reveals only the possibility of bias, the agency should determine whether to permit the member to participate. A member who is excluded from participation in the committee deliberations might nevertheless be invited to offer views as a guest or witness called by the committee. Individual cases should be ruled on by the Commissioner, after consultation with the appropriate center director.

COMMITTEE OPERATIONS

Few written policies exist to guide FDA advisory committee operations. Not surprisingly, substantial variation occurs in the actual use of committees both among and within centers. Some of this variation is justified by the heterogeneity of the subject matter, and the IOM committee wishes to avoid recommending rigid standardization in such cases. As a general proposition, however, substantial uniformity in policies and procedures for advisory committee operations is both desirable and feasible.

The IOM committee recommends that the FDA develop uniform management guidelines for advisory committees applicable across all

three centers and that it eliminate unnecessary differences in the management of committees.

Scheduling Meetings

FDA advisory committee meetings are seldom scheduled more than a few months in advance, and specific agendas are usually a result of the decision to hold a meeting. These practices complicate advance scheduling by committee members of their participation in meetings and advance planning by sponsors of products being evaluated by the advisory committee.

The IOM committee believes that advance scheduling (and accompanying deadlines for such actions as sponsor submissions of data, agency review of an application, and advance distribution of materials to the committee) would allow more effective planning by busy advisory committee members for their participation in meetings and impose greater discipline on the product evaluation process. The committee is aware that such a proposal is not without its "costs"; some of these include the difficulties that would be faced by FDA in advance scheduling of agendas, the heavy demands made on reviewer time, and the potential for compromising the review of the data. Nevertheless, although the IOM committee has not examined in great detail the impact of this proposal on FDA reviewer time or its budgetary implications, it regards the benefits of advance scheduling of meetings and agenda items as outweighing most potential disadvantages.

The IOM committee recommends that FDA adopt a policy of annual advance scheduling of advisory committee meetings and of meeting agendas, with review cycles having deadlines for sponsor submission of data, FDA completion of reviews, and advance distribution of materials to committee members.

Meeting Preparation

General Criteria for Setting the Agenda

The general criteria for determining advisory committee agendas vary from center to center and tend to derive from historical practice as much as explicit policy.

- The 1976 Medical Device Amendments required the Center for Devices and Radiological Health (CDRH) to bring all premarket approval applications (PMAs) to an advisory committee; the center now has some discretion on that issue under the Safe Medical Devices Act of 1990. Based

on its interpretation of what the law requires, CDRH asks advisory committees whether a given PMA should be approved; it does not go beyond this question.

- The Center for Biologics Evaluation and Research (CBER) brings specific product license applications (PLAs) and establishment license applications (ELAs) to its advisory committees, as well as general matters of biologics development. It formulates and asks questions of the committee in much the same way as does the Center for Drug Evaluation and Research. Unlike the other centers, however, CBER also asks its advisory committees to review its intramural research programs and evaluate intramural research personnel.
- The Center for Drug Evaluation and Development (CDER), in September 1991, clarified the range of issues that it might bring to an advisory committee: the approvability of specific drugs; general drug development; issues pertaining to marketed drugs; and the management of the new drug evaluation (NDE) program.[1] Advice on the approvability of specific drugs may be sought on clinical trial design; the data supporting safety, effectiveness, overall risk-benefit, and dosing and scheduling; appropriate surrogate endpoints; other needed studies; postmarketing surveillance; indications for specific populations; and shifts of prescription drugs to over-the-counter status. General advice may be sought on the development of guidelines for classes of drugs, clinical study design issues, and specific safety issues for particular drugs.

The IOM committee commends CDER for this clarification and recommends that CBER and CDRH develop similar statements.

In addressing the management of the new drug evaluation program, the CDER document expands several important aspects of the advisory committee's tasks. Committees may be asked to review periodically (usually annually), first, the pending new drug applications (NDAs) and the major new indications of other drugs in the CDER pipeline; second, the "important products under development," that is, investigational new drugs (INDs); and third, the priorities and resource allocations of CDER's reviewing divisions for the management of INDs, NDAs, abbreviated NDA (ANDA) applications, and supplements to approved applications.

The IOM committee recommends that each center schedule an annual review by each advisory committee of the major NDAs and INDs (or their equivalents) in the pipeline of the respective reviewing division.

Setting Specific Agendas

The IOM committee considered a number of aspects regarding setting committee agendas. For example, the notice of an FDA advisory committee meeting must be published in the *Federal Register* at least two weeks in advance of the meeting; this may require submission for publication by the center at least six weeks before a meeting. An announcement includes a general description of the agenda, for example, the specific NDA of a given sponsor, and the general topics of the meeting; however, this description varies in its specificity.

The IOM committee recommends that the *Federal Register* announcements of scheduled advisory committee meetings routinely include the most detailed statement of the agenda that is feasible within existing time constraints. The IOM committee also recommends that these announcements be sent routinely to advisory committee members when submitted for publication.

The general questions that the FDA must consider in evaluating drugs and biologics are whether, in the determination of safety, the risks of a compound are outweighed by its benefits and whether "substantial evidence" from well-controlled trials exists to support the claims of effectiveness. It would help the review process if advisory committee members were regularly reminded of these decision criteria as they review a sponsor's data.

The IOM committee recommends that the FDA routinely send the general statement of the regulatory criteria governing product evaluation to each advisory committee member in advance of a meeting to assist members in framing their review of the data.

Setting the detailed agenda of an advisory committee meeting and preparing specific questions for it are primarily the responsibility of FDA staff. They are not feasible tasks for committee members themselves to undertake. Yet, the exercise of this responsibility by FDA sometimes results in criticism regarding its apparent efforts to manipulate or influence committee deliberations.

The IOM committee recommends that in the formulation of meeting agendas and of questions, the advisory committee chair be routinely consulted as a standard procedure. It further recommends that committee members be routinely informed that they may modify FDA-

prepared questions, based on their review of the data, and introduce questions of their own before or at an advisory committee meeting.

An issue brought to the attention of the IOM committee was whether FDA questions to an advisory committee should be restricted to scientific and clinical matters or whether they should include the relevant regulatory questions. The IOM committee believes that the scientific and regulatory questions pertaining to an issue are interrelated and that any attempt to presume a distinction between them is artificial.

The IOM committee believes that FDA reviewing units should be free to ask advice on both scientific questions and related regulatory implications, as they deem important.

The FDA is sometimes charged with asking "loaded" or leading questions. The committee has made no determination whether this has occurred. It believes, however, that it is necessary to distinguish between the tone and objectivity of FDA questions and the fact that particular questions may at times indicate the problems that the agency perceives in an application. The committee is not troubled by the fact that precise questions often will reveal the agency's concerns about an application.

The IOM committee recommends that questions asked of advisory committees be fair and objective in tone and avoid language that might be considered biased or inflammatory.

Timely Distribution of Materials

A major complaint of FDA advisory committee members that has been heard for many years is that the agency often fails to distribute materials sufficiently in advance of a meeting to permit their careful review by committee members. Some delays are attributed to limited personnel and administrative resources of the agency, to its natural tendency to complete reviews at the last minute, and to its long tolerance of such practices. Whatever the reasons, the effective and efficient use of advisory committees requires that members receive review materials a reasonable period of time before a meeting.

The IOM committee recommends that the agency adopt and follow a strict schedule for advance distribution of materials. The meeting agenda, sponsor's data and analyses, and agency reviews should be delivered to members at least three weeks in advance of a meeting. The

specific questions for the meeting should be delivered no later than 10 days before a meeting.

In the committee's view, the responsibility for fulfilling this recommendation rests not only with committee executive secretaries, but also with the directors and the application reviewers of the appropriate division. The committee also believes that scheduling committee meetings and agendas in advance should facilitate compliance with this recommendation.

Summaries of Materials Sent to Advisory Committees

The format of materials sent to advisory committee members varies according to how much of an application the FDA decides to send. The materials typically include the sponsor's data, the agency reviews, and the questions to be discussed at the meeting. Although advisory committee members have suggested that the FDA prepare such material in a format that would facilitate its review, the agency understandably resists such "packaging." This major deficiency could be easily remedied, however, by the preparation of concise (20–25 page), complete, and integrated summaries of the sponsor's application and the agency's review.

The IOM committee recommends that the FDA develop a standard format for sponsors to summarize their application briefly yet comprehensively, as well as a comparable format for a summary of the agency's review. These summaries should be provided in addition to the materials normally sent to advisory committee members.

Use of Primary Reviewers

The CDRH assigns primary review responsibility for a particular PMA to one advisory committee member, mainly to obtain a clinical evaluation of the application. The IOM committee believes that this practice can also ensure a more thoughtful committee discussion and that it distributes the work load more evenly among committee members. In addition, the practice has great utility in those situations in which the match between committee expertise and a particular agenda item may be weak. (See the discussion on "custom tailoring" below.)

The IOM committee recommends that the three centers consider the routine assignment of primary reviewers for each application.

Communications Issues

Five types of communication before an advisory committee meeting deserve attention: FDA communication to advisory committee members; communication among committee members; communication between sponsors and members; FDA communication to sponsors; and FDA communication to the public.

First, advance communication by FDA officials with advisory committee members before a meeting has generally been limited to one member at a time, based on an interpretation of the strictures of the Federal Advisory Committee Act (FACA). However, the Chief Counsel to the FDA indicated in a letter to the IOM committee that "such preliminary issues as agenda topics, materials, and questions" could be discussed simultaneously with some or even all members of a committee.

The IOM committee notes this discrepancy between what guides agency practice and the views of the Chief Counsel, endorses the opinion of the latter, and recommends that the FDA clarify its guidance to FDA staff and to advisory committee members.

Second, FDA guidance, based also on an interpretation of the FACA, to advisory committee members has generally been that communication among individual members before a meeting is precluded. Again, the FDA Chief Counsel has written that "preliminary discussions" among committee members do not violate the law.

The IOM committee notes a discrepancy between practice in some parts of the agency and the views of the Chief Counsel, endorses the opinion of the latter, and recommends that the agency clarify the legal bases governing communication among advisory committee members. If, as expected, the Chief Counsel's opinion is adhered to as agency policy, this should be clearly communicated in writing to all FDA personnel who deal with advisory committees, to committee members themselves, and to other interested parties. Preliminary discussions among members for information purposes and to clarify technical issues only should not be discouraged; the limits on such consultations should be clearly defined; committee members should be instructed to document such consultations by a log or other, similar means; and these consultations should be disclosed at each committee meeting.

Third, as a matter of FDA policy, sponsors are discouraged from communicating with advisory committee members before a meeting. The

agency informs sponsors and committee members of this stricture. This policy is designed, in general, to protect the independence of the committee from lobbying by sponsors.

The IOM committee affirms the soundness of this policy.

Fourth, the FDA takes the view that it is not obligated to share with sponsors, or the general public, its communications to advisory committee members before a meeting. The IOM committee, however, believes that it is appropriate for the FDA to provide sponsors with copies of all information that it sends to advisory committees. This practice would facilitate the preparation by the sponsor of its response to agency questions.

The IOM committee recommends that the FDA provide sponsors of applications with the same materials that it sends to advisory committees. Questions should be sent to committees and sponsors on the same schedule.

Fifth, as a general practice, the FDA releases to the public the questions that it has prepared for the advisory committee on the morning of a meeting. The IOM committee agrees with this practice and does not recommend earlier release to the public.

A recent report by Kutak, Rock & Campbell, which dealt with FDA's handling of financially sensitive information, basically concurred that FDA release of the questions to the public on the morning of a committee meeting was sound practice.[2] The FDA has before it the Kutak Rock & Campbell report and this IOM report on advisory committees; it must address the implications of where the two intersect and make any appropriate policy determinations.

Conducting an Advisory Committee Meeting

The successful conduct of an advisory committee meeting involves the conscientious efforts of the committee chair, the members, FDA officials, and the sponsors. To improve the deliberations of advisory committees and the quality of their advice to the FDA, this section recommends a number of steps to be taken regarding the interactions among these parties.

Allocation and Control of Agenda Time

One of the keys to an effective advisory committee meeting is the allocation and control of agenda time. Typically, the initial assignment of

time to agenda items is done by FDA professionals, sometimes in consultation with committee chairs. Once time is allocated, of course, it is important that committee meetings adhere to the established schedule. For this to occur, it is necessary that the chair exercise control over agenda time.

The protection of opportunities for committee discussion is perhaps the primary reason for the chair to exercise strict adherence to the agenda schedule. Discussion time often gets squeezed because it is the last scheduled item on an agenda, sponsor and agency presentations frequently go longer than scheduled, and some committee members may leave to return home.

The IOM committee recommends that the FDA routinely consult committee chairs in the allocation of time to agenda items and that this allocation try to anticipate points throughout the meeting at which committee questioning will be necessary. It further recommends that committee chairs be instructed that the control of agenda time is one of their primary responsibilities, and that they must work to protect committee discussion time, including exercising strict control on the presentations of sponsors and the FDA before the committee as well as attendant questions and discussions by committee members.

Electronic Coverage of Meetings

FDA advisory committee meetings often receive television coverage, which can be intrusive in committee deliberations. FDA regulations governing television or "electronic recording equipment" (21 CFR 10.200–206) vest authority in the advisory committee chair to control such coverage as necessary.

The IOM committee recommends that advisory committee chairs be routinely oriented to their authorities and responsibilities in regard to the control of electronic coverage of advisory committee meetings, for the purpose of facilitating committee deliberations without compromising the public's right to know.

Voting

Voting by CDER and CBER advisory committees occurs at the discretion of the committee chair or according to the tradition of the reviewing division. Depending on the committee, no votes may be taken, votes may be taken only on scientific questions, or votes may be taken only on regulatory questions. All CDRH committees vote on the regulatory question only, i.e., the approvability of a device.

The IOM committee recommends that FDA adopt a policy, consistent across all advisory committees, by which committees are asked for a vote on important questions before the committee. To the extent feasible, the chair should identify in advance the issues on which votes are to be taken.

Agency Neutrality

As a general proposition, the IOM committee believes that FDA staff members should conduct themselves at advisory committee meetings in ways that avoid the appearance of exerting undue influence over the committee. Agency presentations to a committee should focus on the critical evaluation of data but should not withhold or disguise expressions of agency concerns with an application. The tone of agency presentations should be professional, thorough, and dispassionate, and agency staff should not dominate or appear to dominate committee discussions.

Seating arrangements at advisory committee meetings should facilitate committee discussions rather than the convenience of the audience. As a general rule, the IOM committee believes that the division director should not sit next to the committee chair. Nor should other FDA personnel sit among the committee members.

Custom Tailoring of Committee Membership

The FDA has rechartered, or soon will recharter, all of its advisory committees. This will permit agency officials who are organizing a given meeting to draw voting members from any other FDA advisory panel or committee, or from a pool of consultants, on an as-needed basis. Although this "custom tailoring" authority is welcome in principle, it has not yet been used with any frequency, and it poses several challenges to the agency.

In general, the IOM committee believes that the continuity of the standing advisory committee should be maintained and that custom tailoring should be used sparingly to augment a committee's expertise relative to a specific agenda item. On the one hand, the IOM committee recognizes that it may be necessary to add voting members in some cases in which the scientific or clinical scope of a committee may not be adequate for considering a particular class of drugs, biologics, or devices. On the other hand, the frequent use of this flexible authority by the FDA may make it vulnerable to charges of "stacking the deck" with committee members likely to favor its views.

The IOM committee recommends that in cases in which FDA must modify the composition of an advisory committee by "custom tailoring," it do so judiciously and sparingly, augmenting the core committee by adding the needed expertise. The committee also recommends that FDA actively consult the committee chair in the process. It also recommends that the director of the appropriate center approve all such decisions.

Meeting Follow-up

Some FDA centers or divisions provide little or no follow-up to advisory committee members regarding the results of their deliberations. Failure to do so is a source of complaints. A systematic effort to provide follow-up would convey a strong positive message to advisory committee members that the agency attaches great value to their service.

The IOM committee recommends that the FDA follow up each advisory committee meeting by routinely and immediately providing committee members with a copy of all press releases issued after a meeting; informing members by FAX at the time of approval or disapproval of any application that the committee has considered; routinely reporting the status of matters previously considered by the committee at the beginning of each meeting; and reporting annually the disposition of committee-related matters.

ORGANIZATION AND MANAGEMENT

Several prior reports on FDA that deal with advisory committees call for varying degrees of centralization of committee management functions. These reports also highlight the need to address issues of organization and management.

System Management

FDA's technical advisory committees are chartered by the Commissioner of Food and Drugs for the purpose of advising him on the safety and effectiveness of drugs, biologics, and medical devices. In addition, committee members are appointed by him and requests for waivers of conflict of interest are granted by him. Legally, advisory committees report to the Commissioner.

In actual operation, however, the current FDA advisory committee system is highly decentralized and substantial variations exists both across and within centers. These variations have arisen as a result of historical,

organizational, and idiosyncratic influences that are not always rooted in genuine scientific or functional differences among committees. The IOM committee believes that unjustified variation in the use of advisory committees should be minimized in the interest of strengthening their role as independent advisors to the FDA.

This highly decentralized system lacks any agency-wide administrative policy and management guidance. It thus appears vulnerable to controversies that might be avoided or more effectively managed, given a greater agency-wide management capability.

The IOM committee recommends that a high-level official in the Office of the Commissioner of Food and Drugs be assigned primary responsibility for developing, disseminating, and enforcing administrative policy and management guidance to the advisory committees of the three centers.

The directors of the three centers should have explicit responsibilities for managing the advisory committee system. Center directors should implement agency-wide policy for advisory committees; monitor the recruitment of members for technical expertise, source of nomination, and identification of qualified women and minority candidates; personally approve any "custom tailoring" of committees to avert charges that FDA staff are seeking to influence the outcome by the selection of members known to favor a particular view; help design an orientation and training program for committee members; examine issues that arise in a particular committee that may cut across several committees; and support innovation in the use of advisory committees.

Office and division directors of the product review units should also have explicit responsibilities for managing the advisory committee system. They should be actively involved in recruiting advisory committee members, preparing committee agendas, and developing specific questions.

Executive secretaries should report to a central unit within each center. Their responsibilities are primarily to provide administrative support to committee operations. Executive secretaries should also report to the appropriate division director to assist that individual in the program-related work of the committees. The IOM committee recognizes that CDRH executive secretaries differ from those in CDER and CBER in that they are also engaged in the technical review of applications; thus, some comments may not apply to them.

The IOM committee recommends that the executive secretaries report to a central unit in their respective centers for the purpose of providing

administrative support to that center's advisory committees. It also recommends that they report to the appropriate division directors to provide program support to the committees.

In general, the IOM committee believes that a clarification of the roles of all FDA officials responsible for the advisory committee system is long overdue. The objective of this role clarification should be to ensure that advisory committees provide the independent expert advice that the agency requests and needs.

The IOM committee recommends that the roles and responsibilities of all FDA officials involved in the advisory committee system be clearly articulated in agency policy that is widely distributed to FDA professional staff, advisory committee members, and other interested parties. The committee further recommends that the job descriptions of all officials be changed to reflect their respective responsibilities.

Compensation

The authority to set the daily rate of compensation for FDA advisory committees resides with the Commissioner of Food and Drugs. He is subject to four constraints—two legal, one budgetary, and one administrative. The statutory limit on compensation for *all* federal government advisory committee members is the daily rate for a Senior Executive Service IV position, currently $429.50 per day. Regulations of the General Services Administration further limit the daily rate to that of a GS-15 in the General Schedule, currently $320 per day, unless the agency head personally determines that a higher rate "is justified and necessary." The budgetary limit is the obvious requirement that an agency head must have funds to cover the costs of whatever rate is adopted.

Although agency heads have authority to set rates for the members of the committees that advise them, FDA's status as a Public Health Service agency also limits the exercise of that authority. As a practical matter, no single PHS agency can pay advisory committee members at rates much higher than those of the other agencies. Currently, the Centers for Disease Control pays committee members $188 per day, while the National Institutes of Health and the FDA pays $150 per day.

FDA advisory committee members are paid only for those days on which they attend a meeting. The agency is barred by regulation from paying them for homework for normal meeting preparation, even though a member may spend five days or more in preparation. However, CDRH does compensate individual advisory committee members for homework if they conduct an

"agency-directed assignment" that results in a tangible end product, usually a report, that is not the end product of the advisory committee. Typically, this involves using members as primary reviewers of applications. Neither CDER nor CBER compensates committee members for homework in this way.

FDA regulations also permit payment to advisory committee members at the daily rate for travel time that involves 50 percent of an additional day beyond the meeting time and that results in the loss of some regular compensation. However, no use is made of this authority.

The IOM committee believes that all Public Health Service advisory committee members are underpaid, including those who advise the FDA. This is true both with respect to the maximum daily rate allowed by law and GSA regulations and with respect to the opportunity cost to members of foregone consulting fees from drug or device firms of $1,000 a day or more. Moreover, younger members in academic medicine often confront the perception that service on an FDA committee carries less academic reward than that of an NIH study section.

The IOM committee believes that public service should be adequately compensated, although obviously not at the rates of the private sector. It is concerned that the current meager rate of compensation may dissuade some individuals from serving as FDA advisory committee members and may diminish the incentive to others to prepare adequately for meetings. In general, the IOM committee is concerned that these rates do not accurately reflect the value that FDA and the general public attach to the important work performed by advisory committee members.

The IOM committee recommends that the Commissioner, with the Secretary of Health and Human Services, review the adequacy of compensation for Public Health Service advisory committee members, including FDA advisory committee members, and take appropriate steps to maintain daily rates in relation to increases in the federal salary schedule. It further recommends that CDER and CBER, to the extent that they use primary reviewers for applications presented to advisory committees, compensate these reviewers, as CDRH currently does, for "agency-directed" homework.

The IOM committee notes that legislation enacted in October 1992 authorizes the FDA to charge user fees for product evaluation. Under this new authority, it may be appropriate for the FDA to review the compensation of advisory committee members in relation to their contribution to product evaluation.

Orientation and Training

A recurring complaint from advisory committee members has been the absence of an adequate orientation and training program. Although the centers and most divisions have made a number of efforts, no systematic agency-wide or center-wide orientation program has been organized. The IOM committee believes that the need for such a program is clear; program content and organization are addressed in the body of the report.

The IOM committee recommends that the FDA establish a systematic orientation and training program that is directed mainly toward new advisory committee members but that will also be useful for current members and for FDA staff who deal with committees. The Office of the Commissioner should exercise leadership in the design of this program, in cooperation with the three centers. The design should consciously search for agency-wide similarities as well as center-specific and division-specific content. The public service and public health contribution of advisory committee membership should be emphasized in this program.

AGENCY MANAGEMENT AND ACCOUNTABILITY

This report recommends many concrete steps for improving the use of advisory committees by the FDA in the evaluation of drugs, biologics, and medical devices. Throughout the report are general expressions of concern about agency management and accountability, which may not be captured fully by its specific recommendations. Thus, the IOM committee deems it necessary to summarize the latter in relation to these larger considerations.

Agency Management

In the judgment of the IOM committee, it is important to differentiate between the management of the advisory committee system and the management of the product evaluation process as affected by the advisory committee system. Regarding advisory committee system management, the IOM committee's most important recommendation is that a high-level position be established in the Office of the Commissioner to provide administrative policy and management guidance to the advisory committee system. Although the precise location of such an office is properly determined by the Commissioner, an appropriate place may be the Office of the Deputy Commissioner for Operations, to which the directors of the three relevant centers now report.

Advisory committees, the IOM committee believes, have become a permanent fixture in the FDA's evaluation of products, and their effective use should be a responsibility of FDA officials at all levels. Improvements in management would flow from clarifying the roles and responsibilities of all officials involved in the advisory committee system—from the Commissioner through the center, office, and division directors, down to the executive secretaries. Such clarification should include changing the job descriptions of these officials as necessary. The IOM committee acknowledges the important role of FDA office and division directors in the work of advisory committees; it does not recommend circumventing these officials by proposing to locate operational responsibility for committees elsewhere, but urges clarification of their responsibilities for the effective performance of the system.

An orientation program for advisory committee members, which could also be used in training responsible FDA officials, would improve the performance of the entire system. Other management-related recommendations pertain to the recruitment of qualified members and establishment of a pool of potential members; greater involvement by the Office of the Commissioner in conflict of interest issues (both in developing internal FDA policies and procedures and in negotiating with the DHHS Office of the Special Counsel for Ethics and the Office of Government Ethics); and more attention to preparation for and conduct and follow-up of advisory committee meetings.

Various recommendations of the IOM committee address improvement of the product evaluation process and the role of advisory committees in that process. In particular, we believe that advance scheduling of committee meetings and agendas, with attendant deadlines for the sponsor and the agency, would bring greater discipline to the product evaluation process and make more effective use of advisory committees.

The IOM committee recognizes that its recommendations for improved management of the advisory committee system will require additional resources. Therefore, the report provides an estimate of the incremental costs of the IOM committee's recommendations. The IOM committee regards the recommended review of advisory committee member compensation as an important management issue that deserves attention by the Commissioner and the Secretary of Health and Human Services. The compensation of committee members should be reviewed in relation to the newly-adopted user fee system for product evaluation.

Agency Accountability

The FDA as an entity, and not just its component parts, should be accountable for the effective performance of its advisory committee system. The IOM committee's recommendations lead to ways of increasing agency-wide accountability. Here, as in the recommendations above on improving management, the committee emphasizes the importance of designating a high-level official in the Office of the Commissioner who should be responsible for administrative policy and management guidance for the advisory committee system.

It is also important as a component of accountability to recognize that advisory committees are *advisory* to the FDA, and that the authority for decisions rests with the agency. It would be unnecessary to reiterate this basic distinction were it not that some agency critics regard advisory committees as independent adjudicatory bodies that should hear sponsors' views, on the one hand, and agency views, on the other, and decide in favor of one party or the other. Acknowledging this basic authority-advisory distinction should facilitate advisory committees becoming even more effective and influential than they are at present, which the IOM committee endorses.

Consequently, the IOM committee's recommendations emphasize practical ways (especially in Chapter 7) to ensure the intellectual independence of advisory committees. The rationale for this emphasis is to increase the likelihood that advisory committees will render that impartial, expert advice that the agency and the public should expect.

A CONCLUDING RECOMMENDATION

In the conduct of this study, the IOM committee has discovered the multifaceted complexity of the FDA advisory committee system. It has benefited from many thoughtful letters, memoranda, and communications on aspects of this complexity. As a result, the committee believes that its report could serve to increase agency accountability for the advisory committee system.

The IOM committee recommends that the Commissioner circulate this report widely within the FDA, to all advisory committee members, and to other interested parties. It also recommends that the report be submitted to the Secretary of Health and Human Services and to the appropriate committees of the Congress for the purpose of seeking concurrence of goals and budgetary support for the implementation of the report's recommendations.

NOTES

1. Memorandum from Bruce Burlington, M.D., Deputy Director for Scientific and Medical Affairs, to Carl C. Peck, M.D., Director, and Gerald F. Meyer, Deputy Director, Center for Drug Evaluation and Research, "Advisory Committees. Policy and Practices in Selection of Agenda Items to be Considered by Center for Drug Evaluation and Research Advisory Committees," September 1991.

2. Kutak, Rock & Campbell. *FDA Safeguards Against Improper Disclosure of Financially Sensitive Information*. Final Report. Washington, D.C., November 14, 1991.

1

Introduction

On July 1, 1992, the Food and Drug Administration (FDA) had a total of 41 technical advisory committees or panels that supported the work of the three centers responsible for the evaluation and regulation of drugs, biologics, and medical devices.* In 1991, these committees met a total of 67 times, usually for two days per meeting, for an average of 3.2 meeting days per year. They typically consist of seven to nine members each, none of them employees of the FDA, who are supported by FDA professional staff and by a number of consultants. In this report, we refer to these advisory committees and their administrative support as the FDA's *advisory committee system*.

FDA technical advisory committees play an important, multifaceted role in the development and evaluation of new drugs, biologics, and medical devices. Although they are involved to some extent in the early stages of product development, and sometimes in postmarketing issues, their primary use lies in assisting the FDA to evaluate specific applications for marketing approval—new drug applications (NDAs) for drugs and biologics, product licensing agreements (PLAs) for biologics, or pre-market approvals (PMAs) for medical devices.

In addition, FDA advisory committees help the agency develop general guidelines regarding scientific and technical issues related to the agency's broader regulatory responsibilities, most often for biologics and less often for drugs and devices. In the case of the Center for Biologics Evaluation and Research, they review intramural research programs and personnel.

Although the advice of advisory committees is not binding on the FDA, the recommendations of a committee are widely regarded as a predictor of agency action. As a result, FDA advisory committees have become highly visible to the public, the Congress, the media, and the financial investment community. A committee meeting involving a particularly controversial matter may draw an audience of 300 to 400 individuals, including FDA staff,

* These centers are, respectively, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH).

sponsor employees, observers from competitor firms, the national and trade press, including cable and network television, and investment advisors.

The importance and visibility of FDA advisory committees make this study a timely effort. The Institute of Medicine (IOM) committee that conducted it hopes that its analyses and recommendations will be useful to the agency and to the public in helping the FDA fulfill its responsibilities to the American people.

ORIGINS OF THE STUDY

The study originated in remarks made by Dr. David A. Kessler, the Commissioner of Food and Drugs, at a meeting of the IOM's Forum on Drug Development in March 1991. Before his appointment as Commissioner in late 1990, Dr. Kessler had chaired the Subcommittee on Drugs and Biologics of the Department of Health and Human Services (DHHS) Advisory Committee on the Food and Drug Administration (known as the Edwards Committee, after its chairman, former Commissioner Dr. Charles E. Edwards). In that capacity, Dr. Kessler had heard testimony that challenged the credibility of the FDA's advisory committee system, and, to the Forum members, he expressed the desire to make more effective use of these committees.

The resulting interaction between the IOM and the FDA led to this study. That interaction began when the FDA requested that the IOM examine the optimal use of FDA advisory committees in the evaluation of drugs, biologics, and medical devices. The agency also asked the IOM to consider their use in relation to agency management and agency accountability.

In response, the IOM appointed a committee to conduct the study. Its members brought expertise in medical research; development of drugs, biologics, and medical devices; design and conduct of clinical trials; medicine, surgery, and nursing; regulation of drugs, biologics, devices, consumer products, and health care services; administration of medical research, health care financing, and the delivery of health care services; and health and science policy research. Three members of the IOM committee currently serve on FDA advisory committees, two others have served in the past, and three were previously involved as FDA officials in the design of the current system.

In the early months of the study, two meetings were held between the committee chair, Dr. Laurence E. Earley, and the Commissioner, the second involving the acting president of the IOM and senior IOM staff. These meetings were held to clarify certain questions about the scope and purpose of the study. Then, when the study committee convened for its first meeting

on December 6–7, 1991, it heard a personal presentation from Commissioner Kessler of his views on the study.

The Commissioner made three major points at the December meeting. First, he indicated that the improved use of advisory committees was one of several management improvement initiatives that he was undertaking. Consequently, he asked for a report that would provide him and the FDA with operational guidance. Second, he expressed his hope for the deep involvement in this study of FDA senior staff, a hope that has been realized in committee deliberations and in the study's data collection efforts. Finally, he emphasized the importance of the IOM committee's addressing the process for controlling financial conflict of interest because it was affecting the operations of the advisory committee system.

STUDY OBJECTIVES

The purposes of the IOM study that arose out of the initial FDA request, the concerns of Commissioner Kessler, and the deliberations of the study committee are the following:

- To understand the FDA's process of product development and evaluation so that the IOM committee could recommend how best to use advisory committees in the context of the FDA's overall mission, policies, and procedures.
- To understand how FDA advisory committees are used in the three centers responsible for the evaluation of drugs, biologics, and medical devices.
- To provide the FDA with operational guidance regarding the selection of advisory committee members and the operation and management of the advisory committee system.
- To study and analyze the impact on the use of advisory committees of financial conflict of interest statutes, regulations, and administrative practices, and the related issue of scientific bias.
- To consider the use of advisory committees for improving agency management and increasing agency accountability.

SCOPE OF THE STUDY

This study examines the use by the FDA of *technical* advisory committees in the review of therapeutic and diagnostic medical products—drugs,

biologics, and devices.* Prior studies have usually dealt with FDA advisory committees that are used for the evaluation of drugs or sometimes drugs and biologics; they have seldom included medical devices. This study encompasses the use of advisory committees by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH).

The study considers the use of *policy* advisory committees only in passing. It does not examine any advisory committees serving the Center for Food Safety and Applied Nutrition, the Center for Veterinary Medicine, or the National Center for Toxicological Research. The study also excludes the Board of Tea Experts, a technical advisory committee created by the Tea Importation Act of 1897 to advise the Commissioner regarding standards for imported teas.

Other limitations of the study should be mentioned here. This was a relatively short study by IOM standards. The contract ran from September 23, 1991, until October 22, 1992, during which the committee met only four times. As a result of this timetable, the IOM committee focused its attention on matters that it considered to be of greatest concern to the agency and to the advisory committees themselves, with two consequences worth noting here.

First, although the committee's report (in Chapter 6, "Ensuring Committee Integrity") deals with both financial conflict of interest and intellectual bias, the former receives the lion's share of attention and for very practical reasons. The committee was asked by the FDA to consider the problems of regulating the potential financial conflict of interest of advisory committee members, mainly because these issues were threatening to impair the agency's ability to use advisory committees. Moreover, the existing statutes regulating conflict of interest deal solely with financial conflict.

Second, intellectual bias, which is important in its own right, was considered by the committee but received less commitment of committee time than did financial conflict. For one thing, the legal principles operative in this context are a matter of some uncertainty. The statutes governing conflict of interest do not address intellectual bias. And although the Federal Advisory Committee Act does require that advisory committee membership be "fairly balanced," the meaning of this for technical advisory committees cannot be specified easily in advance of a specific meeting agenda. Even though intellectual bias has yet to generate for the FDA the administrative difficulties that have characterized the matter of financial

* The definitions of drugs, biologics, and devices are discussed in the Appendix to this chapter.

conflict of interest, the IOM committee recommends that agency begin now to address this issue.

In recent years, research universities and scientific journals have been among the institutions actively pursuing the general issues related to intellectual bias. But the treatment of bias by scientific regulatory agencies in relation to advisory committees remains undeveloped. A study of greater scope (than just the FDA) and of greater duration would have been required to plough this new ground.

THE ROLES OF FDA ADVISORY COMMITTEES

In general, advisory committees are the major way by which the FDA obtains independent technical and scientific advice. Other means for obtaining such advice include workshops, symposia, consultants, and extensive, often informal, contacts among agency professionals and the scientific and medical communities. Although this report focuses on advisory committees, the IOM committee recognizes and endorses the appropriate use of these other means of obtaining independent expert advice.

The IOM committee believes that it is essential for the FDA to systematically acquire independent external scientific advice. The scope of the agency's regulatory responsibilities is so vast and its involvement in leading-edge scientific and technical matters so deep that the agency cannot maintain contact with the frontiers of science and medicine without such expert advice. Hence, it is critical that the FDA avail itself of all means of obtaining such advice of which technical advisory committees are one.

When the FDA began using external sources of technical advice, following the 1962 drug amendments to the Food, Drug, and Cosmetic Act, it did so to compensate for the limited technical capabilities of its professional staff. Today, however, the situation is much changed, and for the most part the agency has a highly trained, scientifically qualified professional staff. In this context, the FDA obtains external advice, whether from advisory committees, workshops, or consultants, to complement the capability of its professional staff.

The FDA initiated an advisory committee system in the early 1970s to provide technical assistance related to the development and evaluation of drugs, biologics, and medical devices. The system was also designed to lend credibility to the agency's decisions and its decision-making processes. In addition, it was a means by which the FDA could provide a forum for public discussion of certain controversial issues.

In general, the IOM committee believes that the existing FDA advisory committee system is fundamentally sound, has served the agency well, and does not need wholesale reorganization. It should be retained and strength

ened. However, later in this report, the committee recommends a number of administrative and procedural changes that are designed to improve the performance and usefulness of the system.

The IOM committee believes that the primary role of FDA advisory committees is and should be to provide independent expert scientific advice to the agency in its evaluation of specific drugs, biologics, or medical devices at any stage of consideration by the agency. A related role is to advise the FDA on general criteria for evaluation and on broad regulatory issues that are not related to a specific product.

Several key terms warrant further comment. First, *independence* refers to freedom from influence by the sponsor of the product under consideration, by any other entities or persons that could gain or lose as a result of the outcome of the process, and by the FDA itself. However, the focus of concern about committee independence has changed over time. For example, in 1976, the Fountain Committee (see Chapter 4) believed that committees might be too independent of FDA professional staff and subject to the influence of drug sponsors. By 1990, the concern was the opposite: it was claimed by some that advisory committees were subject to excessive influence by the FDA's reviewing divisions.

The high stakes associated with FDA decisions mean that parties disappointed by the agency's action have strong incentives to charge that the independence of advisory committees is compromised by undue FDA influence. Yet, the issues of independence and undue influence are quite elusive and pertain to many facets of the process—for example, the recruitment of committee members, delays in advance distribution of materials, the content and tone of agenda questions, and seating arrangements. The IOM committee makes recommendations on all of these issues, the direction of which points to greater safeguards of the independence of committees.

Second, *expert scientific advice* implies that members of advisory committees will be acknowledged experts in some technical or scientific field that is relevant to the purview of the specific advisory committee.

Third, advisory committees *advise* the FDA and do not themselves have authority to make decisions that obligate the agency or any private party to a course of action.

Fourth, advisory committees respond to specific questions that have been identified by the professional staff of the agency. These questions may deal with study design or methodology, adequacy of data, and assessment and interpretation of risks and effectiveness.

Finally, although advisory committees have a prominent role in the product licensing stage, they are sometimes used earlier in the product development cycle and sometimes invited to consider postmarketing issues.

The IOM committee believes that it is proper for the FDA to use committees at any stage of review when scientific advice is needed.

PRACTICAL LIMITS ON THE USE OF ADVISORY COMMITTEES

It is important to acknowledge that there are significant practical limits on the FDA's use of advisory committees. The most important general limit is the amount of time that committee members are able to commit to the activity (measured in meetings per year, days per meeting, days of preparation per meeting, and travel time). The amount of resources that the FDA has available to support advisory committees also limits their use. In Appendix A, we estimate the additional resources that the FDA will require to implement the recommendations of this report. The IOM committee recognizes that resources for advisory committees must be considered in the context of overall FDA budget priorities and that there is widespread concern about the adequacy of the agency's budget to meet its growing statutory responsibilities.

There are also specific limits on what any given advisory committee meeting can accomplish. One such limit is the necessity for the agency to be selective in choosing questions for committees from an enormous amount of material under review. Another is the difficulty faced by an advisory committee chair in attempting to control agenda time at meetings, with the consequence that committee discussion time is often severely truncated.

THE FEDERAL ADVISORY COMMITTEE ACT

FDA advisory committees operate within the legal framework of the Federal Advisory Committee Act (FACA). The post-World War II era, and especially the 1960s, saw the evolution of widespread use of advisory committees by many federal government agencies. In 1972, Congress enacted the FACA to regulate this development. Although not written primarily for technical advisory committees, the FACA was passed and became effective just as the FDA was beginning to make extensive use of such committees. It provides the statutory framework for all federal advisory committees, including those of the FDA.* Because references to the FACA are made throughout this report, we describe it briefly at this point.

The FACA incorporates three conflicting themes. One concern of Congress was to introduce uniform procedural standards for federal advisory committees.[1] The other congressional objectives were to promote an open, transparent process and to reduce the number of advisory committees. These

* Certain advisory committees are excepted by law or are subject to special requirements.

themes reflected a concern in the U.S. Senate that industry-oriented advisory committees, acting in closed meetings, had assumed too large a role in agency decision making.

The major requirements of the FACA are as follows. To form an advisory committee, an agency head must:

- determine that it is necessary and in the public interest,
- consult with the General Services Administration (GSA),
- file a GSA-approved charter, and
- announce its formation in the *Federal Register*.

Committees must be rechartered every two years using the same procedures.

The FACA requires a formal nomination process for advisory committee members, including a *Federal Register* solicitation; that committee membership be "fairly balanced" and that meetings be announced in the *Federal Register* 15 days in advance and be open and provide for public participation.* The original FACA openness requirement was reinforced in 1977 by the Government in the Sunshine Act, which requires that deliberations of government collegial bodies, including advisory committees, occur in open session.

The FACA also requires that a federal official oversee all advisory committee meetings, including calling a meeting, approving the agenda, being present at all times, and adjourning the meeting if necessary. Detailed records—minutes and a transcript—of advisory committee meetings must be kept. Unless exempted under the Freedom of Information Act, these records are available to the public.

STUDY METHODS

The IOM committee that conducted this study drew on several sources of information and used a variety of methods in its analysis.

- The committee met on four occasions, in December 1991 and in February, May, and August 1992. These meetings were two days long, except for the final meeting, which was a one-day executive session.
- Three IOM committee members had been personally responsible for designing and managing the FDA advisory committee system in prior

* A meeting may be closed only if a basis exists for invoking one of several exceptions. In the case of the FDA, these exceptions are, as a practical matter, restricted to the discussion of proprietary or trade secret information or to matters involving confidential information about individuals. Only the Commissioner can make the decision to close a meeting.

capacities as FDA officials. They thus provided the committee with an invaluable historical perspective and a keen sense of agency dynamics.

- Five members of the IOM committee had served or were serving on FDA advisory committees in the areas of drugs, biologics, and medical devices and thus brought direct experience to bear on the IOM committee's deliberations.
- The IOM committee and its staff interacted with senior FDA professionals throughout the study. This included the participation of the latter in the first three meetings of the IOM committee; three half-day meetings with leaders of the CDER, CBER, and CDRH (mentioned below); and individual meetings of the IOM committee chair with the directors of the CDER, CBER, and CDRH, as well as with the Deputy Commissioner for Operations and the Senior Advisor to the Commissioner. In addition, project staff had several large meetings on FDA premises with senior FDA staff in January, April, and June 1992, as well as many smaller meetings.
- The IOM committee also organized three work groups to conduct its activities. One work group consisted mainly of the academic clinical members of the committee, and these individuals personally interviewed nearly 50 current or former FDA advisory committee members.
- Another committee work group dealt mainly with FDA officials. It held three half-day meetings in February, respectively, with the leaders of the CDER, the CBER, and the CDRH.
- The Industry Liaison Panel, convened by the IOM committee, was established to obtain the views of the pharmaceutical, biotechnology, and medical device industries on FDA advisory committees. It drew its members from the prescription drug, over-the-counter drug, biotechnology, and medical device industries. Its report, a useful input to the IOM committee, was widely circulated to the FDA, consumer organizations, and other interested parties and, in turn, elicited very useful commentary.
- The third work group, on industry and consumers, held a half-day meeting with the Industry Liaison Panel to discuss the latter's report.
- The IOM project staff contacted consumer organizations, including all members of the FDA Consumer Consortium, and solicited their views on advisory committees. They also conducted interviews later with several consumer organization representatives.
- The IOM committee sent a letter to a number of food and drug attorneys who had experience with the agency or with clients who dealt with the agency, soliciting their views on FDA advisory committees. The committee received several useful responses.
- The IOM project staff interviewed the executive secretaries of all FDA advisory committees across the three centers (CDER, CBER, and

CDRH). They also interviewed the CDER office and division directors responsible for advisory committees.

- Numerous meetings or telephone conference calls were held between members of the IOM committee and its staff and representatives of the FDA, the Department of Health and Human Services, and others. These included the Division of Ethics and Program Integrity, the Office of Consumer Affairs, senior FDA staff, the Chief Counsel of the FDA, the DHHS Special Counsel for Ethics, and the Office of Government Ethics.
- IOM project staff, at the direction of the committee, requested information from FDA staff on numerous occasions. These requests were typically fulfilled with dispatch and efficiency.
- IOM project staff compiled an extensive collection of documents pertaining to FDA advisory committees, on which the committee drew in preparing its report.
- The study also drew on information from a concurrent FDA survey of the members of drug advisory committees by the Office of Planning and Evaluation.
- The study commissioned papers on the following topics: the use of advisory committees in drug, biologics, and device approval in the United Kingdom, France, Germany, the Netherlands, and the European Community; a history of the Anti-Viral Drugs Advisory Committee; the federal conflict of interest statutes; the Federal Advisory Committee Act; and the prospects for and problems with early involvement of advisory committees in the product evaluation process. These papers are not printed in this report; nevertheless, they all provided useful input to the work of the committee.

In January 1992, at a meeting that followed the IOM committee's first meeting, FDA senior staff advised the IOM staff of the necessity to conduct interviews with key FDA personnel. Although the amount of raw data on FDA advisory committees was enormous (e.g., lists of members, agendas, meeting transcripts, and other such materials), very little had been analyzed or digested, much less shaped into a manageable form.

Even so, the committee and its staff were unprepared for the extent of variation in practice regarding advisory committees that exists among and within centers. As one committee member put it, "On no occasion when two or more centers were present in the same meeting was there a single answer to any question." Although the report refers frequently to this phenomenon, no attempt has been made to document the extent of variation among the centers in their use and management of advisory committees. To have done so would have required an enormous data collection effort, with quite uncertain benefits. The IOM committee instead has addressed itself to the need for an increased measure of consistency and standardization across and

within centers in instances in which no programmatic or functional reason for variation could be identified.

REPORT ORGANIZATION

This report is organized into three parts, which are divided into eight chapters. Part I, Overview, includes the summary of the report and this chapter. The summary includes all of the study's recommendations. Part II, Background, constitutes an historical account of the evolution of the FDA advisory committee system (Chapter 2), a description of the current system (Chapter 3), and, in Chapter 4, a consideration of the recurring issues that pertain to the advisory committee system.

Part III, The FDA Advisory Committee System, addresses the matters on which operational guidance was requested. Chapter 5 deals with committee membership issues of recruitment, nomination, and appointment and briefly with potential financial conflict of interest. However, Chapter 6 is devoted to the subjects of financial conflict of interest and intellectual bias as these issues affect the operation of advisory committees. Chapter 7 deals with a number of operational issues related to advisory committees. Chapter 8, in turn, considers matters involving the organization and management of the advisory committee system.

A NOTE ON CROSS-NATINOAL COMPARISONS

It is often the case in discussions of the FDA, especially in the area of drug evaluation and regulation, that reference is made to European countries that provide for faster introduction of new drugs to the market. For example, the practices of the Committee on Safety and Medicines (CSM), an advisory body serving the Department of Health and Social Services' Medicines Control Agency in the United Kingdom, are often held up as an alternative approach to that of the FDA.

The IOM committee, in support of this study, commissioned a very thoughtful paper on the use of advisory committees in drug and device approval in the United Kingdom, the Netherlands, Germany, France, and the European Community.[*] In all countries save the Netherlands, an official government agency makes the decision about approving drugs, biologics, and, in some cases, medical devices for introduction to the market. The

[*] This paper, "Advisory Committees in the Approval Process of Drugs in Europe," was prepared by Laurie M. C. Faro, Ph.D., J.D., Department of Health Policy, Erasmus University, Rotterdam, The Netherlands. It is available from the Institute of Medicine Division of Health Sciences Policy.

Netherlands has a commission of part-time, nongovernment experts, and this body makes the official decisions to approve new drugs.

Although there are potentially interesting lessons to be learned from cross-national comparisons, it is impossible to disentangle the issue of the use of advisory committees from the larger political, economic, and institutional questions of product evaluation and regulation. The IOM committee decided that the pursuit of cross-national comparisons in the use of advisory committees, however intriguing, would take it too far afield from its charge to provide the FDA with operational guidance on its use of technical advisory committees.

APPENDIX

For its purposes, the IOM committee has adopted operational rather than formal scientific or legal definitions of the three groups of products whose regulation and review are the subject of this report. Our report considers "drugs" to be those products that are reviewed and regulated by FDA's Center for Drug Evaluation and Research and, correspondingly, "biologics" those regulated by the Center for Biologics Evaluation and Research and "devices" those regulated by its Center for Devices and Radiological Health. These operational definitions obviously match the administrative responsibilities of the FDA.

There do not appear to be well-established scientific definitions of these three product groups. There are, however, official regulatory definitions in statute or agency regulations. The FDA's structure parallels the dichotomy that the law draws between drugs and devices, but the distinction between drugs and biologics chiefly reflects historical factors and, in turn, administrative convenience. Although biologics are formally regulated mainly under the so-called Biologics Act of 1902, now Section 351 of the Public Health Service Act, they also fit the definition of "drug" in the 1938 Federal Food, Drug, and Cosmetic Act, and are also subject to some controls based on the later law.

The situation is further complicated, from a technical legal perspective, because some medical products may integrate as components both drugs (or biologics) and devices, making them potentially subject to the separate legal requirements applicable to each category. These dual-class or combination products have sometimes provoked jurisdictional conflicts among the three centers within the FDA. However, the agency, acting under requirements of the Safe Medical Devices Act of 1990, has in the past year adopted new regulations for dealing with combination products and product jurisdiction issues and has negotiated three inter-center agreements in support of these regulations.

Drugs are defined in Section 201(g)(1) of the Federal Food, Drug, and Cosmetic (FDC) Act, as amended, mainly by the criterion that they are "articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them [which are] intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." This definition is broad enough to encompass biologics for regulatory purposes; the statute also specifies that this definition "does not include devices or their components, parts, or accessories."

Biologics are defined under Section 351 of the Public Health Service Act as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man." The meaning of these terms is elaborated in (21 CFR 600.3(h).

Devices are defined in Section 201(h) of the FDC Act as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes." This definition also includes "devices intended for use in the diagnosis of conditions other than disease, such as pregnancy, and in vitro diagnostic products, including those previously regulated as drugs."

NOTE

1. Bruce L.R. Smith, *The Advisers: Scientist in the Policy Process* (Washington, D.C., The Brookings Institution, 1992).

2

Historical Evolution of FDA Advisory Committees

The Food and Drug Administration is responsible, among other things, for ensuring the safety and effectiveness of drugs, biologics, and medical devices. Its scientific and regulatory responsibilities in these areas arise from different historical periods, derive from different statutory bases, affect different industries, and are embedded in different organizations and processes. Its responsibilities encompass investigational drugs, biologics, and devices; the evaluation and regulation of new products; postmarketing surveillance of some products; licensing of establishments; oversight of manufacturing processes; product labeling and advertising of prescription drugs and restricted devices; and other functions.

Public advisory committees are used widely throughout the federal government for a wide array of purposes.[1,2] They are subject to the provisions of the Federal Advisory Committee Act (FACA). As used within the FDA, such committees may be ad hoc or standing; they are further classified as policy advisory committees and technical advisory committees. The former advise on "broad and general matters"; the latter deal with "specific technical or scientific issues, which may relate to regulatory decisions before FDA (21 CFR 14.1(b)(2), 1991). In this report, we are primarily concerned with standing technical advisory committees to the FDA that deal with drugs, biologics, and medical devices. Only brief consideration is given to policy advisory committees.

The Code of Federal Regulations (CFR) sets forth the FDA's definition of the primary characteristics of an advisory committee:

> An advisory committee ordinarily has a fixed membership, a defined purpose of providing advice to the agency on a particular subject, regular or periodic meetings, and an organizational structure, for example, a chairman and staff, and serves as a source of independent expertise and advice rather than as a representative of or advocate for any particular interest (21 CFR 14.1(b)(5), 1991).

The FDA uses technical advisory committees of outside scientific experts to advise it on the approvability of specific products and on the scientific and clinical policy issues it confronts regarding product development and evaluation. The agency also uses these committees to legitimate the soundness of its analysis of a given product, as a public forum for discussion of controversial issues, and, on occasion, as an "appeals court" for disputed agency decisions.[*]

This chapter recounts the history of FDA advisory committees as it has evolved along somewhat different pathways for drugs, biologics, and medical devices. Variations are due partly to the differences in regulatory responsibilities in these areas and partly to the administrative entities and their cultures. At the end of the chapter, a brief section contrasts FDA advisory committees with the study sections of the National Institutes of Health.

The FDA initiated the use of advisory committees in the 1960s and 1970s for the evaluation of drugs. It extended their use in the early 1970s to the review of biologics soon after the Division of Biological Sciences of the National Institutes of Health was transferred to the FDA as the Bureau of Biologics. Finally, following the Cooper report of 1970, FDA in the early 1970s began to use such committees to classify medical devices, a step that Congress later mandated in the Medical Device Amendments of 1976 for both classification and product evaluation purposes.

DRUGS

The FDA's use of agency-chartered advisory committees for drug evaluation has evolved over the three decades since the 1962[**] drug amendments to the Food, Drug, and Cosmetic Act. Those amendments required FDA to assess all new drugs for effectiveness, in addition to safety (as required by the 1938 amendments), and to reassess for effectiveness

[*] The FDA does not consider the following to be advisory committees: (1) an internal committee composed exclusively of full-time federal government employees, even if it includes one or two consultants who are special government employees; (2) a group of persons convened on an ad hoc basis to discuss a matter of current interest to the FDA but that has no continuing function or organization and involves no substantial preparation; (3) a group of two or more FDA consultants meeting with the agency on an ad hoc basis; (4) a group of experts employed by a private company or trade association that has been asked by the FDA to provide its views on a regulatory matter before the agency; and (5) a consulting firm hired by the FDA to provide advice on some matter (21 CFR 14.1 (b)(4, 5, & 7), 1991).

[**] In contrast, the use of study sections by the National Institutes of Health began in the period immediately following World War II as that agency's extramural research program came into existence.

nearly 4,000 prescription drugs that had been introduced to the market between 1938 and 1962—before proof of effectiveness was required.

The FDA responded by seeking external advice from the National Academy of Sciences-National Research Council (NAS-NRC) on previously marketed prescription drugs, establishing its own review committees for over-the-counter drugs, and extending such committees to new prescription drugs. The evolution of this use of outside scientific experts, recounted by Cooper for the 1960s, is briefly summarized here and then discussed at greater length below for the NAS-NRC Drug Efficacy Study and for the OTC review.

The Thalidomide controversy brought the teratogenic, mutagenic, and carcinogenic effects of drugs to public and scientific consciousness and provided a powerful stimulus for enacting the 1962 drug amendments. In partial response, Commissioner George Larrick established an Advisory Committee on Teratology. He also established an ad hoc committee to review the new drug application for Enovid, the first oral contraceptive. [*]

Dr. Joseph Sadusk, Jr., director of the Bureau of Medicine (predecessor to CDER) under Larrick, created a Medical Advisory Board and a series of standing and ad hoc advisory committees. His justification for the latter was to broaden the flow of communication to the bureau director beyond the immediate, full-time staff, there being no way in Sadusk's judgment for the FDA to acquire all of the staff expertise needed for drug evaluation. He hoped that advisory committees would upgrade the quality of inputs to the evaluation process. Sadusk visualized open advisory committee discussions, with industry scientific and medical personnel present, along with a representative of the American Medical Association's Council on Drugs, and executive sessions involving only committee members and FDA staff.

Dr. James Goddard, who succeeded Larrick as Commissioner in 1966, suspended the development of these ad hoc advisory committees and reviewed their use. Subsequently, Goddard and Dr. Herbert Ley, initially director of the Bureau of Medicine and then Commissioner, reactivated a program for standing advisory committees in 1967. In August 1967, the agency established a number of committees for drugs, with staff support of one medical officer and one executive secretary provided by the Division of Research and Liaison. One particularly active committee was the Obstetrics and Gynecology Advisory Committee, chaired by Dr. Louis Hellman. The

[*] A policy committee, the National Advisory Food and Drug Council, was established in March 1964, under Larrick, to address trends in science and technology and related economic, demographic, and political developments. This group met first in December 1964, but its use declined under successive Commissioners, and it was disestablished in 1968.

Anti-Infective Agents Advisory Committee, chaired by Dr. Calvin Kunin, was also active.

Cooper, analyzing the 1960s experience with advisory committees, observed that the dynamic of committee deliberations depended on the personality of the committee chairman, the advance preparation of agenda materials by staff, the significance of the items that came before the committee, and the extent to which FDA staff genuinely wished to obtain independent inputs. These same questions remain salient today, as this report indicates.

In 1969, a new Republican administration took office and placed FDA Advisory committee operations on hold while it reviewed the agency's resources and assessment capabilities. It permitted the Obstetrics and Gynecology Advisory Committee to continue its work, and the committee consequently issued its second report on oral contraceptives in August. In December 1969, Dr. Charles Edwards became Commissioner and, within a relatively short time, reactivated standing advisory committees in the following program areas: anti-infective agents, biometrics and epidemiological methodology, cardiovascular and renal disorders, dermatology, endocrinology and metabolism, food standards, methadone maintenance, neuropharmacology, obstetrics and gynecology, psychomimetic agents (jointly with the National Institute of Mental Health), radioactive pharmaceuticals, and respiratory and analgesic drugs.

This periodic use of advisory committees in the 1960s eventually led to the present prescription drugs advisory committee system, which is currently administered by the Center for Drug Evaluation and Research (CDER). Two other events helped form the system: the Drug Efficacy Study of the mid-1960s and the review of over-the-counter (OTC) drugs in the 1970s. These developments are reviewed below. Importantly, not one of these efforts was required by the Food, Drug, and Cosmetic Act; each was initiated by the FDA as a way to implement key portions of the statute.

Drug Efficacy Study

The Drug Efficacy Study, conducted by the NAS-NRC at the request of the FDA, began in mid-1966 and concluded in 1969. The study came about because the 1962 drug amendments required, among other things, that drugs approved between 1938 and 1962 on the basis of safety alone be reviewed for their effectiveness as well. Commissioner Goddard, in a March 31, 1966, memorandum to Dr. Keith Cannan, director of the NAS-NRC Division of Medical Science, wrote:

> Although this is a one time task requiring evaluation of material somewhat different from that now obtained in current drug approval procedures, its long range significance exceeds that of all other drug activity currently pursued by the Food and Drug Administration. Recommendations from the most expert sources are essential if this Administration is to suppress flagrant claims, eliminate worthless products and at the same time protect the physician's therapeutic resources.[3]

Goddard indicated that the FDA had estimated that there were 3,000 marketed products for which applications had been filed in the 1938–1962 period and perhaps another 1,000 that were being marketed without applications. These products involved only a fraction of this number of chemical moieties; the agency estimated their sum as between 300 and 400, which could be grouped into about 60 categories of therapeutic effect. "These categories," Goddard wrote, "could be combined into ten or twelve groups, each group being appropriate for consideration by a different panel of experts."[4] Thus, the Drug Efficacy Study began with the judgment by the FDA that expert outside advice was required. Goddard saw no conflict between the NAS-NRC effort and existing FDA advisory groups. The latter, he wrote, "are not equipped to undertake a task of this magnitude and cannot be expected to alter their other activities to the extent that would be required."[5]

What is also interesting in retrospect is that Goddard also wrote that no problems were anticipated with conflict of interest:

> The Food and Drug Administration is prepared to accept the principle of professional integrity whereby panelists with personal interest in a therapeutic entity will not personally participate in deliberations where their personal interest is involved. Likewise FDA is confident that professional personnel of the caliber utilized on NAS-NRC panels would not put information obtained from panel discussions to improper use in other activities conflicting with the interests of FDA.[6]

The NAS-NRC responded favorably in April, and the two parties signed a contract in mid-June. Indicating the agency's eagerness to get under way, a May 1 FDA press release announced the study:

> The FDA sought the assistance of the NAS-NRC in carrying out the efficacy study because of that group's unique ability to tap the top medical and other scientific talent of the Nation. NAS-NRC sponsorship also will assure an objective, independent review. The FDA itself does

> not have sufficient medical personnel to carry out a project of this scope, Dr. Goddard said. Recruiting on a temporary basis the skilled scientists required was not considered feasible, he added.

The NAS-NRC proposed that a Policy Advisory Committee be established to develop guidelines for the review panels, of which there were to be approximately 30.[7] The committee consisted of 29 members and the chairmen of an initial 27 evaluation panels.[8] This body met in July with medical and pharmacy professionals, the pharmaceutical industry, and the FDA, and generated procedural guidelines for submission of data on drugs under review. The 27 panels (later increased to 30) were staffed by 10 Public Health Service physicians assigned to the NAS-NRC effort by the FDA. Each panel had 6 members.

The Policy Committee, in consultation with the appropriate chairman, assigned drugs to a panel for review. Each panel was asked to designate a reviewed drug as effective, probably effective, possibly effective, or ineffective. The factual basis for these determinations was to be information submitted by sponsoring firms, the medical literature, information supplied from FDA files, and the experience and judgment of panel members.

According to a 1968 report, 237 firms submitted a total of 3,637 drug preparations for review;[9] a later report put the figure at 2,824.[10] According to the latter, most were prescription drugs, but about 15 percent were over-the-counter products; two-thirds were single-entity drugs, the rest were combinations. The panels completed their work in 1968, and in 1969 the NAS-NRC submitted reports to the FDA on more than 2,800 drugs. Each panel, it was estimated, reviewed approximately 150 drugs.

Although the reports of the Drug Efficacy Study were only advisory, in the sense that FDA retained both the authority to disagree and the responsibility for all implementing decisions, they were often decisive in the agency's decision making. Implementation, however, required that the FDA formally accept the study's recommendations; if it decided to withdraw approval for a drug, it was obliged to announce its plan to do so and afford the sponsor an opportunity to respond.

How was the NAS-NRC Drug Efficacy Study received? In retrospect, its reception appears to have been mixed. Apparently, the study earned some respect from the pharmaceutical industry, in part because the expeditious review contrasted with current industry concerns about the length of FDA reviews of new drug applications. However, because the study recommended the withdrawal of some products from the market, litigation resulted. This generated advice to the FDA that the recommendations of the advisory panels not be accorded undue weight.[11] For example, Warren Whyte, senior attorney for Abbott Laboratories, wrote:

> In my view, [the NAS study reports] are *opinions* rendered by groups of eminent scientists on the effectiveness or ineffectiveness of drugs. Although, because of the basically secretive manner in which the NAS review was conducted, we do not know very much as to how the panels proceeded, it does appear fairly clear that each member of the panels could not possibly have reviewed the New Drug Applications, the clinical studies, and the literature on each of the many drugs before each panel.[12]
>
> He quoted Dr. Louis Lasagna, a principal in the Drug Efficacy Study, who stated in an affidavit that "the findings of the NAS-NRC panels should not be regarded as final, conclusive, or irrevocable scientific determinations, decisions, or recommendations."[13]

In a similar vein, in 1971, Rodney Munsey, then associate general counsel of the Pharmaceutical Manufacturers Association, offered the following judgment:

> Many people have erroneously assumed that the recommendations [of the NAS-NRC Drug Efficacy Study] submitted were, in fact, official recommendations of the NAS-NRC or of the Drug Research Board [of the NAS]. They were not. The NAS-NRC appointed 30 panels of six members each to review the evidence on the drugs involved. Many panel members were not affiliated with the Academy or the Council. The recommendation transferred to FDA concerning any particular drug was not an Academy-Council product, but was only a consensus recommendation of the six-man panel. It was not reviewed by the Academy, the Council, or anyone on the Drug Research Board. Some panels reviewed hundreds of drugs and, of course, every member was not, and did not claim to be, an expert on each and every drug. Further, every member did not have the time to consider the merits of each dry reviewed. Many decisions were made by split vote and compromise.[14]

Over-the-Counter Drugs

Although the Drug Efficacy Study dealt primarily with prescription drugs, the NAS-NRC panels also considered 420 over-the-counter drugs (out of a total of 3,500 drugs reviewed).[15] In 1972, the FDA faced the mammoth problem of reviewing all of the OTC drugs that had been marketed between 1938 and the enactment of the 1962 Drug Amendments. Its solution was to establish an OTC review system. This review focused on ingredients, not finished individual products, and on assessing those that were "generally

recognized as safe and effective" (GRAS/E) and that were not misbranded. The regulatory product of this process was a series of monographs consisting of approved active ingredients, labeling, and other general requirements.

A regulation promulgated in May 1972 described the administration of this OTC review system, which included four phases.[16] The critical first phase was the review of OTC ingredients by expert panels responsible for specific product classes (e.g., analgesics). This was followed by publication of a proposed monograph on the basis of the panel recommendations; publication of a tentative final monograph, based on the agency response to comments on the proposed monograph; and the issuance of a final monograph.

To launch the first phase, the FDA established 17 panels of expert advisers to review the literature, data, and studies that applied to the labeling and active ingredients for 27 categories of OTC drugs. Its intent was to give credibility to the OTC review by having outside experts bring their independent judgments to bear on the safety and efficacy of every active ingredient in the OTC marketplace. A related objective in establishing the panels was to handle a heavy workload, for which the FDA staff were limited in number and scientific competence.[17] Indeed, in this instance, the basic role of the FDA staff was to administer the OTC panel process.

Each panel had three types of members: seven scientific voting members, one nonvoting consumer member, and one nonvoting industry representative. The scientific voting members included physicians, pharmacologists, and toxicologists from both active medical practice and academia; for the most part, however, these individuals were subspecialty academic physicians, depending on the drug category. Approximately 185 experts served on these panels, assisted by another 74 experts. All served as special government employees.[18] The OTC Drug Division managed all of these panels; in essence, this was its major function.

Baumgartner's history of the OTC review concluded that the FDA grossly underestimated the size and complexity of the panel phase, which lasted 10 years. The panels reviewed, by therapeutic category, 722 individual active ingredients that had 1,454 active uses in the hundreds of thousands of marketed OTC drug products; in the process, they evaluated more than 14,000 volumes of submitted data and other scientific materials. Collectively, the panels met more than 513 times on more than 1,050 calendar days, and their deliberations spanned an average of 4.5 years each.

This system, which was heavily influenced by Peter Barton Hutt, FDA Chief Counsel at the time that it was established, articulated some general principles of FDA advisory committees. Such committees should include nonvoting industry and consumer representatives, for example, to increase the likelihood that the results of the review would be accepted in both

quarters. The participation of the former helped to avoid surprising the industry, to maintain contact with it, to detect problems early, and to minimize opposition.

The OTC review advisory committees operated under the Federal Advisory Committee Act (adopted in 1972), federal conflict-of-interest statutes, and, before the review was finished, the Government in the Sunshine Act. This environment of openness and public scrutiny was very different from that of the Drug Efficacy Study and much more characteristic of our present period.

Prescription Drug Review

In the early 1970s, following the episodic efforts of the prior decade, an advisory committee system evolved for prescription drugs. Its purpose was to secure expert advice on the evaluation and approval of new therapeutic products. A number of controversial cases influenced the design of this system. One concerned the drug Promalin,[*] for which the Bureau of Drugs established an ad hoc committee to review the data about its approval. The expert committee heard presentations from industry, the American Academy of Allergy, and the FDA staff.

Dr. Charles Edwards, then Commissioner of Food and Drugs, sat through this entire meeting. Afterward, he instructed the FDA staff to create similar advisory committees for all drug areas. His main aim was to ground the regulatory process in the mainstream of science; he also hoped to generate some protective cover for agency decisions and to establish a sound review process.[19]

The purpose of the committee system that was established was to advise the FDA on drug approval decisions and on guidelines for drug development in order to bring credibility to approval decisions and to enhance their quality. Advisory committees served both as consulting groups and as open forums for discussing controversial issues, a function that the agency considered particularly important.

The FDA used internal memoranda to create these prescription drug advisory committees administratively. Subsequently, the agency promulgated general regulations governing the formation and operation of advisory committees, which are now codified in (21 CFR 14). In general, from one to three committees advised each of the six to eight FDA prescription drug products divisions. The advisory committee system that emerged during this

[*] Dr. Marion Finkel remembers it as the Maternal Health Committee, not the Promalin Committee.

period fulfilled the continuing function of reviewing new drugs, unlike the backlog-clearing task of the OTC review.

Management of these committees has not always been without controversy, as the Fountain Committee report of 1976 (see Chapter 4) makes clear. Nevertheless, in these early years, the FDA did learn the importance of asking precise questions, of formulating fixed agendas, and of reaching closure on what the committee actually thought—usually by soliciting a vote. Committee members later felt that they had been well or badly used as a function of how well the FDA performed these tasks.[20]

The FDA created a system of standing, rather than ad hoc, committees so that committee members would see the fruits of their labor.* Terms for advisory committee members were four years but were often shortened by such factors as slow appointments and early departures. Committee members were primarily academic physicians, although it soon became clear that other expertise was also needed. As a result, most committees have had a statistician, some have an epidemiologist, and occasionally a committee has a toxicologist member.

In the late 1970s, the FDA added consumer representatives to its prescription drug advisory committees. This arrangement did not work well, because such representatives were frequently at a scientific disadvantage in discussions with other committee members. Subsequently, the agency began to appoint technically qualified, consumer-nominated members to drug advisory committees, which provided the FDA with qualified experts with personal ties to the consumer community. (Chapter 5 discusses this topic at greater length.)

Summary

In the Drug Efficacy Study, the FDA turned to the NAS-NRC to obtain access to independent expertise through an organization whose modus operandi was expert committees. In doing so, it sought to clear a large backlog of work—for which it lacked adequate staff—in a short period of time. It learned in implementing that study's recommendations the practical limits of time and resources, and the consequent inability of expert advisory panels to review all relevant data. They agency learned as well that it was not relieved of the responsibility to decide issues. Most important, however, the

* The agency had been criticized earlier for forming ad hoc committees, bringing in experts, obtaining advice, and then discharging the committee. These critics maintained that such a system produced the appearance of external expert review without the reality, in addition, the advisers disappeared and never learned the results of their work.

study established the pattern within the FDA of seeking outside expert advice on major decisions.

Several noteworthy differences between the Drug Efficacy Study and current FDA practices can be noted. For example, having charged the NAS-NRC, the FDA turned the review task over to the NAS-NRC; it had no role in selecting panel members, and the composition of panel membership originally was not disclosed. The panels met in secret, and the frequency and location of their meetings were not known. Indeed, the FDA at first was not willing to disclose the study reports. In addition, the federal conflict-of-interest requirements were not applicable, and the NAS's own procedures were not very stringent by today's standards.

The FDA set up the OTC review panels to bring independent expert judgments to decisions about the safety and efficacy of over-the-counter drugs. A key objective of the review was to generate outcomes that the agency could enforce. A secondary justification for the action was that the panels were needed to take over a workload that was too great for the FDA staff to handle and that it was not competent to handle.

The prescription drug review process evolved to assist the FDA in its continuing work of reviewing new drugs. As such, it departed from the large-scale, one-time efforts of the Drug Efficacy Study and the OTC drug review. The drug advisory committees were intended to ensure the scientific soundness of the agency's regulatory decisions, to establish the credibility of the process, and to provide a way to air controversial issues.

In each of these efforts, the FDA initiated the use of advisory committees. The Drug Efficacy Study suggested a model, and the OTC review moved advisory committees under the direct management of the FDA. Prescription drug review activities incorporated advisory committees into the continuing operations of the agency in its review of new drugs.

BIOLOGICS

The federal government regulated biological products intended for human use even before it began to regulate drugs and medical devices. In the United States, biologics regulation dates to the Virus, Serum, and Toxins Act of 1902 (later expanded and consolidated in the Public Health Service Act). Drug regulation began some four years later with passage of the Food and Drug Act in 1906; it was extended substantially in 1938 and then again in 1962. Comprehensive device regulation did not receive explicit statutory underpinning until 1976.

The biological products covered by the 1902 act were those that had come into general use by that time—that is, viral vaccines, bacterial vaccines, antitoxins and toxoids. (It is of some historical interest that the Biologics

Act also included arsphenamine and its derivatives and other trivalent arsenic compounds, because at that time there was no existing separate statutory provision for the regulation of drugs.) Later, as blood and blood fractions and allergenic extracts came into medical use, they, too, were regulated as biologics. Thus, Section 351 of the Public Health Service Act, as currently amended, defines biological products as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man."[*]

The main use of early biologics was to control communicable diseases, a public health purpose logically pursued by the government. Indeed, the development and regulation of biological products are embedded in a public health rationale and public institutional context. As a result, in the early years of this century, national governments, states, and sometimes even cities were involved in the production and use of biologics through public laboratories. No equivalent of today's industrial capability in biologics, biotechnology, or drugs then existed; one public health task was to create such a capability. These public health origins of biological products give a distinctive cast to this area of regulation.

In the United States, responsibility for regulating biologics was initially assigned to the U.S. Public Health Service and to the laboratories that later came to be the National Institute of Health (NIH). In the post-World War II National Institutes of Health, biologics regulation was originally part of the Microbiological Institute; the NIH created a separate Division of Biologic Standards (DBS) in 1956.

The NIH years of the biologics program left several legacies. First, the present-day Center for Biologics Evaluation and Research (CBER) is a regulatory unit deeply embedded in a medical science research organization. Its professionals engage in both the regulation of biological products—inspecting manufacturers and sampling vaccine production lots—and scientific research dealing with biological products, often in collaboration with the laboratories of other public health agencies. The aims of this research are to improve existing products and, in some cases, to explore the feasibility of developing new ones. Other tasks include the development of new tests for determining safety and efficacy and the production of laboratory reference standards.

On occasion, the FDA's biologics organization has also conducted clinical trials of either experimental or licensed products (sometimes in collaboration with other NIH components or the Centers for Disease

[*] See Appendix, Chapter 1.

Control). Its research and regulatory decisions are tied to similar programs in the biologics control laboratories of other nations through the World Health Organization (WHO) and its Committee on Biological Standards, as well as through the various WHO working groups that report to the Committee on Biological Standards.

This extensive involvement with the public health community and the scientific research community created a climate favoring the seeking of scientific consensus in regulatory decision making. For example, the lengthy development of a major new product, such as a vaccine, includes the organization of numerous national and international scientific workshops and conferences. The biologics regulatory organization typically was the organizer of these conferences, often with joint sponsorship by interested components of other public health agencies here and abroad. Although these conferences did not provide advice on specific regulatory decisions, they contributed data and discussions that often influenced the development of requirements for the product and, in the process, generated international consensus about standards. *

During the years in which the biologics regulatory program was a component of the NIH, ad hoc advisory committees were sometimes formed to deal with matters of high public visibility, such as a major new product that was being considered for approval or an important problem that occurred with an existing marketed product. The membership of these committees generally included experts from government as well as the academic community. Although the work of a committee might extend over a period of months or years, its charge was limited to advising on the particular product or problem under review. Committee members would routinely participate in any pertinent workshops or conferences and be familiar with laboratory programs of the DBS. Thus, they acquired great understanding of the issues before the committee. Ad hoc committee meetings were closed to the general public. Initially, these committees reported to the Surgeon General of the Public Health Service; later, they reported to the Director of the NIH.

Historically, manufacturers of biological products have submitted license applications as "rolling submissions"; that is, they submitted portions of the application during the entire development process, with supplements added as additional studies are completed. Consequently, unlike most new drug applications, an application for a biologic typically was reviewed in its parts long before it was formally submitted in complete form. Thus, any ad hoc committee would usually meet on several occasions to review a product (or

* Because the WHO has long been deeply involved in biologics, standards discussions in this area were always international.

group of similar products) under development before all of the studies needed for licensure had been completed. By the time of licensure, the committee would have had ample opportunity to become familiar with all research data relating to the product and would have participated in the development of the regulatory requirements for it. The Surgeon General's ad hoc live poliovirus vaccine advisory committee, for example, had many meetings and participated in a number of conferences over an extended time before the licensing decision arose. During this time, both the committee and the agency's scientific staff had formed close working relationships with the research personnel of the potential manufacturers of the vaccine, as well as with other scientists in the national and international public health communities involved in poliovirus vaccine research.

In this same period, licensing applications for lesser biological products usually received no outside attention and were reviewed and acted on solely by the staff of the biologics regulatory organization. Thus, the ad hoc committees had substantial involvement with certain high-visibility products, but they provided no comprehensive oversight of the overall regulatory program or of biologics development generally.

The other use of advisory committees by the biologics program that developed at the NIH and has been extended to the FDA was in the review of intramural research. (No comparable function exists for advisory committees of the other two FDA centers, the centers for Drug Evaluation and Research and for Devices and Radiological Health.) Just as each NIH institute had one or more standing committees for the review of intramural research, the DBS had its "board of scientific counselors," experts who reviewed the quality and appropriateness of intramural biologics research as well as the qualifications of individual scientists and made recommendations to the Director of the DBS. The DBS specifically charged the review committee not to review regulatory matters. The current CBER advisory committees continue this tradition.

In the early 1970s, the Division of Biologic Standards at the NIH came under fire from Senator Abraham Ribicoff's Subcommittee on Government Operations. The DBS and the NIH management did not fare well in the ensuing controversy. This embarrassed the Nixon administration, which inspired the administrative transfer of the biologics regulatory function from the NIH to the FDA. Thus, in the summer of 1972, the DBS was transferred from the NIH to the FDA, and renamed the Bureau of Biologics. The intention of the move was to strengthen the division's regulatory role and dilute the public health emphasis. The FDA itself had become a component of the Public Health Service in the 1960s. Yet despite its transfer to the FDA, many of the CBER's present policies, procedures, and practices stem from its years within the NIH. For example, CBER headquarters and its

principal laboratories continue to be located on the NIH campus, and it has maintained extensive research contacts with the NIH.

The transfer was followed by a number of management changes in the biologics organization and a decision to reexamine the efficacy of all existing licensed biological products. At that time, there were no standing committees for biologics regulatory decisions, and the ad hoc committees that were involved had a narrow focus. To carry out its regulatory functions, the bureau created a process similar to the comprehensive OTC drug review and formed six standing committees to review the principal categories of biological products: major vaccines, bacterial vaccines, blood products, and products for which the science base was substantially less, such as allergenic extracts.

Each committee had approximately seven scientifically qualified voting members who were expert in the particular area under review. In addition, the bureau chose a nonvoting "consumer" representative and a nonvoting "manufacturing" representative for each of the panels. These committees had FDA staff support and were responsible for reviewing licensed products and making recommendations to the Commissioner about those that did and did not meet contemporary standards of efficacy. (Safety was considered indirectly because it bore a relation to efficacy.) The process, which was quite similar to the OTC review, began in late 1972 and early 1973 and took several years.

The scale and scope of the review were substantial in both administrative and logistical terms. As the committees began their work, it became apparent that these same experts could be helpful to the agency in other ways: giving ongoing advice about new products (assuming the role of earlier ad hoc committees in this regard); advising on general problems that occurred with both marketed and experimental products; and reviewing intramural research similarly to the function of the NIH DBS Board of Scientific Counselors. As the agency completed its one-time comprehensive reviews of existing products, it reduced the number of these original committees and rechartered them to provide continuing advice on all of the organization's regulatory and research programs.

In 1982, the biologics bureau was consolidated with the Bureau of Drugs into the Center for Drugs and Biologics. This arrangement lasted five years; the FDA separated the two units in 1987 into the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research.

MEDICAL DEVICES

The use of advisory committees by the Center for Devices and Radiological Health (CDRH) differs from that of the CDER and CBER in

one critical aspect: it is required by statute. The Radiation Control Act of 1968 mandated the establishment of the Technical Electronic Products Radiation Safety Standards Committee (see the later discussion), which was the first acknowledgment by Congress that advisory committees could be useful in the administration of food and drug law. It was the Medical Device Amendments of 1976, however, that required the extensive use of advisory committees as an integral aspect of the device regulation authorized by that act.

The Cooper Report

In an October 30, 1969, message to Congress on protecting the interests of consumers, President Richard M. Nixon called for "certain minimum standards" for medical devices and declared that "the government should be given additional authority to require premarketing clearance in certain cases [of medical devices]." In response, the Secretary of Health, Education, and Welfare (HEW) appointed a committee to study the regulation of medical devices and to recommend a legislative program to implement the President's message.

The Study Group on Medical Devices of the Department of HEW issued its report, *Medical Devices: A Legislative Plan*, in September 1970.[21] This committee and its report were known as the Cooper Committee and Cooper report, respectively, after the chairman, Dr. Theodore Cooper, then Director of the National Heart and Lung Institute of the NIH. Among the committee members were Dr. Charles Edwards, Commissioner of the FDA, and Dr. Mark Novitch, then Special Assistant for Pharmaceutical Affairs, Office of the Assistant Secretary for Health and Scientific Affairs, and later Deputy Commissioner and Acting Commissioner of the FDA.

The committee's charge was to recommend procedures for establishing standards for certain medical devices and for the review and regulation of other devices before marketing. It found three issues central to a sound legislative proposal: (1) an immediate and systematic review of all devices "available and in use" in order to group them in one of three categories—those that should be exempt from standards and premarketing review, those for which standards should be established to ensure "safety and reliability," and those requiring premarketing review; (2) delineation of an acceptable plan "for assuring expert scientific review of the safety and effectiveness of medical devices at the clinical application phase" and before marketing; and (3) defining the government's role in standard setting and enforcement.[22] Regarding classification, the report recommended that "appropriate scientific, health, and engineering experts" be organized to conduct the initial review of existing devices and to advise on their

classification. For premarketing review, it recommended the establishment of "standing permanent advisory scientific review panels ... to assist in the review of data on new medical devices and to advise the Secretary of their safety and effectiveness." In addition, the report recommended that the Secretary be granted authority to certify existing standards or establish new ones and to audit manufacturers for compliance. It noted that prior experience with the initial and long-term safety and effectiveness of medical devices was often limited, that device development was dynamic, that hazards arose from use as well as from design and manufacture, and that existing data were quite inadequate.

Although various private organizations had tried to provide manufacturers with standards in specific areas, these efforts were poorly financed and coordinated, were not comprehensive, and lacked the force of law. The FDA was the only government agency with authority to regulate all medical devices, but its authority was limited to preventing misbranding and adulteration. Although the courts had recently upheld the agency's efforts to regulate certain devices through drug premarketing controls, the scope of this authority had not been clearly defined. Manufacturer concerns for product liability further underlined the need for "a system of device regulation."

Consultants to the Cooper Committee agreed that "the public deserves more protection," but they regarded drug regulation as an inappropriate model that was likely to inhibit innovation if applied to devices. However, the approaches favored by the consultants ranged from self-regulation to insistence on Good Manufacturing Practices to premarketing notification to premarketing approval, and did not reflect consensus.

The report noted "that a system of 'peer group' review of scientific data would induce confidence within the medical device community that decisions related to devices and standards were soundly based." The basic logic regarding the use of outside experts, whether for classification, standard setting, or premarketing review, was spelled out as follows:

> The variety of medical devices already in use are produced from an equally wide variety of materials. Moreover, the bases of scientific data range from almost pure empiricism to reasonably well systematized information. As a result, there are many scientific and technical issues involved in the evaluation of medical devices that require judgment by expert professionals all along the developmental continuum from research through development to testing, evaluation, and preparation for sale. Accordingly, unilateral decisions by government agencies without expert advice would be as unwise as unilateral decisions by developers or producers. Instead, this study recommends that regulation of medical

> devices be accomplished with the recognition that scientific problems should be solved scientifically, with sound scientific advice provided to the Federal authority exercising the responsibility essential to effective control.[23]

To summarize, the Cooper report recommended that three categories of devices be established—those "so well recognized as safe and effective" that neither standards nor premarketing approval was needed, those that could be regulated by standards, and those "new and unproven critical devices that are at the leading edge of technological innovation and biomedical explorations" and that required premarketing review. For the latter, it recommended that the Secretary be authorized to establish standing advisory panels "generally patterned along clinical sub-specialty lines, composed of appropriate experts from the physical and biological sciences, engineering, medicine, and dentistry qualified to evaluate medical devices." These panels should be permanent, meet regularly, have appropriate regulations governing conflicts of interest, and advise the Secretary about the acceptability of each device for clinical application or marketing. The report also recommended that a Medical Devices Advisory Council should be available to the Secretary for policy issues related to medical devices and should include experts in device development and representatives of manufacturers, users, and patients.

On the basis of the Cooper report's recommendation, the FDA initiated an inventory of medical devices and began classifying medical devices that were already on the market.[24] Two pilot panels—one for orthopedics and another for cardiovascular devices—met in November 1971 to develop a system for classifying devices, and by late 1972, the FDA had indicated its intention to classify all devices over the next 12 to 18 months with the aid of outside expert panels.[25] The agency also announced that it was initiating efforts to develop device standards.

The Medical Device Amendments of 1976

In the period following the Cooper report, a broad consensus developed regarding the need for increased legislative authority over medical devices. The FDA authority to regulate drugs as devices was cumbersome, time-consuming, and inadequate. The consensus was stimulated in part by manufacturers seeking to alleviate their concerns about product liability.[26*]

[*] One appendix to the Cooper report was a lengthy law review article on product liability, which listed 10 pages of representative court cases on defective medical and surgical instruments.

The legislative process moved slowly, culminating in new legislation six years after the Cooper report. In early 1976, the House Committee on Interstate and Foreign Commerce issued its report on pending device legislation. It reviewed the contents and recommendations of the Cooper report in detail. In addition, it approvingly noted the several references of the Cooper report to "peer review" groups for review of scientific data about devices, consisting of representatives from industry, the federal government, the academic community, and other concerned organizations, including consumers.

The House Commerce Committee, drawing on the Cooper report recommendations, "and in an effort to afford the [FDA] the best possible scientific advice and expose the agency's decisions to public scrutiny," drafted a bill that relied heavily "on the proceedings of experts, with ultimate authority vested in the Secretary." This proposed legislation provided for classification panels, which were to use the prior FDA classification panel efforts and review them "in light of the statutory classification criteria." It also provided for establishing advisory committees for product approval evaluation.

The Medical Device Amendments, which were enacted in late 1976, were heavily influenced by the Cooper report. They required the creation of advisory panels or committees for two purposes. The first was the classification of medical devices (Section 513). Following adoption of the amendments, the FDA revisited the classification process in accordance with the act. The new classification advisory panels had the benefit of prior efforts, which were a useful point of departure.

The second purpose was the evaluation of medical devices regulated by risk tier. Class I devices required no standards or premarketing review. Class II devices were to be regulated by performance standards (Section 514). Class III devices required premarketing approval (Section 515). Given that no performance standards have been issued by the FDA since the 1976 amendments, it is chiefly the premarketing approval process of Class III devices that concerns the IOM committee.

For product evaluation, the amendments called for establishment of permanent advisory committees. To these advisory committees the FDA was to appoint "persons qualified in the subject matter to be referred to the committee and of appropriately diversified professional backgrounds"; the agency was also mandated to appoint a chairman and provide necessary clerical support. The performance standards section called for the appointment of nonvoting consumer and industry members; this provision was omitted from the premarketing approval section, but the practice was

adopted for the product review committees nevertheless and is the basis for current policy.*

Although the Safe Medical Devices Act of 1990 modified the original 1976 legislation in certain respects—giving the agency greater discretion in the use of advisory committees—it did not change the basic mandate to use such committees. For example, the 1976 amendments required the FDA to bring all pre-market approvals (PMAs) to advisory committees; now it has discretion to do so after "the fourth device of a kind" has been approved.

In addition to the requirements of the medical device amendments, the Center for Devices and Radiological Health administers the 1968 Radiation Control for Health and Safety Act, which is a section of the Public Health Service Act. Congress enacted this legislation to protect the public against the dangers of electronic product radiation through the development of performance standards for controlling the emission of such radiation. Implementation of this law required the creation of the Technical Electronic Product Radiation Safety Standards Committee (TEPRSSC).

In 1990, the CDRH rechartered its advisory committees into a single Medical Device Advisory Committee with a number of panels. Concurrently, the agency implemented the combination products requirements of the Safe Medical Devices Act by issuing regulations on product jurisdiction (which encompassed combination products) and negotiating three intercenter agreements on this subject. The CDRH rechartering of its device advisory committees converged with these product jurisdiction efforts and led to a rechartering of CDER and CBER advisory committees as well. These developments are reviewed in greater detail in Chapter 3.

NIH STUDY SECTIONS

It is worth contrasting FDA advisory committees with the study sections of the National Institutes of Health, if only because academic medical scientists are very familiar with the latter and often extrapolate these experiences to the operations of the former. The functions of the two sorts of committees, and the contexts in which they operate, are quite different. The pertinent distinctions are these:

* Section 520 of the device law also mandated the creation of a manufacturing process advisory committee to advise the FDA on the methods, facilities, and controls used for the manufacture, packaging, storage, and installation of a device. The device Good Manufacturing Advisory Committee consists of nine members: three employees of federal, state, or local governments, and two each representing the device manufacturing industry, physicians and health professionals, and the general public.

- The 21 original NIH study sections were announced in late 1946; they had clear policy purposes and relatively simple administrative needs related to the review of extramural research grant proposals by academic scientists and the awarding of grants.[27] As discussed earlier, FDA advisory committees have a more recent history, are used for multiple purposes, and lack the academic science constituency of the NIH study section system.
- An NIH study section is responsible for reviewing a number of research grant proposals in their entirety. In contrast, the FDA review of a new drug application (NDA), a product license application (PLA), or a pre-market approval (PMA), involves a larger, more complicated application. Moreover, such a review is the legal responsibility of the FDA and, as a practical matter, cannot feasibly be performed by an advisory committee.
- A research proposal may take several days to review; an evaluation of a product application (NDA, PLA, or PMA) requires months or even years.
- A study section reviews only documents and hears no presentations, but an FDA advisory committee hears sponsor and FDA presentations and sometimes other experts.
- FDA medical reviewers develop detailed knowledge of a given application and often firm judgments regarding it, based on their own views of what constitutes good science and good medicine. (FDA executive secretaries in drugs and biologics are unlikely to develop an independent view of the merits of a proposal; in devices, they often are also proposal reviewers). By contrast, although NIH executive secretaries may have a sense for good science, they are not formally responsible for more than the efficient performance of the study section.
- FDA professional staff incur few costs if they hold up an application but confront great pressures to reach the "right" decision. In contrast, it is expected that all research proposals received by the NIH by a certain date will be reviewed at a specified time and that the study section will determine what is "right" in terms of scientific merit, technical feasibility, budget, and priority.
- Although medical scientists care intensely about study section reviews, society is largely uninterested in which scientist gets what research dollars. By contrast, society is not indifferent to the recommendation of an FDA advisory committee on the public availability of a medical technology (as evidenced by the press and television coverage of such meetings).

Thus, as will be clear throughout this report, FDA advisory committees differ in important policy, administrative, and operational respects from the more familiar NIH study sections.

SUMMARY

A number of themes can be identified in the historical development of the use of advisory committees by the FDA. Among the most prominent are the following:

- FDA leadership took the initiative in introducing advisory committees for the review of drugs and biologics; these committees were not imposed on the agency by the Congress. The device amendments, which do require such committees for evaluation of medical devices, constitute congressional recognition of their importance for the agency.
- In the case of the Drug Efficacy Study, the OTC drug review, and the biologics review, these committees fulfilled major workload functions —clearing a backlog of work for which the agency lacked adequate personnel—and provided independent expertise. Over time, they came to play a central role in the assessment of new products and technologies.
- The use of advisory committees in the biologics program involved the review of intramural research programs and personnel, in addition to product evaluation. In addition, in vaccine development, the committees were used throughout the product development cycle and participation included scientists from other units of the Public Health Service as well.
- For medical devices, the anticipated uses of advisory committees were product classification, standard setting, and review of new products. The initial classification panels did their work and were not continued; the function is now fulfilled by product review panels. The standard-setting function did not develop as anticipated and committees, save the Technical Electronic Product Radiation Safety Standards Committee, were not used for this purpose. The primary purpose of device advisory committees today is the review of new products.
- In the FDA setting, advisory committees play a supportive role to agency professionals. They do exercise great influence in agency decisions, but their role as advisers is more literally so than is the case for NIH study sections.

NOTES

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16. Ibid.
17. Presentation by J. Richard Crout, M.D., to the IOM committee, December 6, 1991. Crout served at the time as director of the FDA's Bureau of Medicine.
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23. Ibid.
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26. Edward M. Swartz, "Products Liability. Manufacturer's responsibility for defective or negligently designed medical and surgical instruments," *De Paul Law Review* 18(2 & 3, Summer 1969):348–407.
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3

The FDA Advisory Committee System

This chapter describes the current advisory committee system of the Food and Drug Administration. It first provides an overview and then considers the official purposes of such committees. It also examines their actual uses, including the variations in use among the different centers and the complementary ways that the agency obtains expert advice. The chapter also discusses the "goldfish bowl" environment within which FDA advisory committees function.

THE PRODUCT EVALUATION PROCESS

The three units of the Food and Drug Administration that concern us in this report are the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH).The work of the three centers is mainly but not exclusively related to the evaluation of new therapeutic and diagnostic products. The discussion in this chapter is frequently organized around the three different categories of medical technologies—that is, drugs, biologics, and devices.

The Drug Evaluation Process

When, after in vitro testing and animal studies of toxicity, a new chemical entity appears promising enough to consider clinical trials in humans, the sponsor must notify the FDA of its intention to conduct such trials.[1] The investigational new drug (IND) application that the sponsor files contains both current data and details of the study design. The FDA, on receipt of an IND, has 30 days within which to review the submission. If the agency judges that no safety problems bar the initiation of the trial, it may allow the IND to become effective and the trial to go forward. If problems exist, it may place a "clinical hold" on the trial until the sponsor corrects

the problem or withdraws the application. If the FDA does not respond within the 30-day period, the sponsor may begin the clinical trial.

Drug development involves three stages of clinical trials. In a Phase I trial, a relatively small group of healthy volunteers take the drug for several months to provide initial data on safety and the drug's action in humans. If Phase I results are acceptable, one or more Phase II trials will be initiated. Phase II trials assess the effectiveness of the drug, with continued attention to safety and noncritical side effects, and define the clinical endpoints for the assessment of Phase II and III data. Phase II studies may involve up to several hundred participants who have the disease under study, compared with 20 to 100 healthy individuals in Phase I trials, in which subjects are often randomized.

If Phase II results are promising and the substance is not being evaluated for the treatment of a life-threatening or serious disease—and therefore being considered for expedited approval (e.g., technologies to treat cancer or AIDS)—then Phase III trials are undertaken.[*] These trials are both larger (several hundred or even more patients) and longer (one to four years). Often, initiation of Phase III trials occurs after a meeting between the FDA and the drug company sponsoring the trial and the FDA to clarify and agree on the basis for evaluating the drug.

The results of Phase III, because of the larger pool of patients and longer duration of use, provide the detailed information necessary for use of the drug in clinical practice—appropriate dosage levels, less frequent side effects, and so forth. The manufacturer submits the data from all three clinical trial phases and from the preclinical studies to the FDA in a new drug application (NDA) to market the substance for specific indications. An NDA also contains detailed information on the laboratory formulation and chemistry of the drug, the manufacturing process, quality control procedures, the proposed labeling of the drug, and samples of the drug in its proposed dose and form.[**] The data from all three phases, but particularly those from Phase III, form the basis for the FDA's decision on approval, including its specification of indications and other parts of the official label.

[*] The FDA issued proposed regulations in April 1992 for the accelerated approval of drugs for serious or life-threatening illnesses (57 *Federal Register* 13234, April 15, 1992). At the same time, the Public Health Service announced a final policymaking promising investigational drugs for AIDS and other HIV-related diseases more widely available under "parallel track" procedures (57 *Federal Register* 13250, April 15, 1992).

[**] In general, only prescription drugs go through the NDA process.

The Biologics Approval Process

The approval process for biologics is quite similar to that for drugs,[2] in part because the FDA merged the two Bureaus of Drugs and Biologics from 1982 to 1987 into the Center for Drugs and Biologics. Biologics, however, are regulated under a regime based on the Public Health Service Act of 1944 rather than the Food, Drug, and Cosmetics Act. Although the evaluation process parallels the drug evaluation process, manufacturers submit a product license application (PLA) rather than an NDA. They do so on a "rolling submission" basis beginning before the end of Phase III clinical trials, submitting pieces of the application as they are completed without waiting to assemble a complete application. In addition, manufacturers also submit an establishment license application (ELA). If the FDA approves the product, both the product and the manufacturing establishment receive licenses.

The Device Approval Process

For regulatory purposes, the FDA classifies medical devices for human use into one of three risk-related categories, as required by the Medical Device Amendments of 1976. All three classes of devices are subject to "general controls," which are "sufficient to provide reasonable assurance of safety and effectiveness" of a device. General controls empower the FDA to:

- prohibit adulterated or misbranded devices;
- require domestic and foreign device manufacturers and initial distributors to register their establishments annually and list their devices;
- ban certain devices;
- demand notification of risks and require repair and replacement of refund for defective products;
- restrict the sale, distribution, or use of certain devices; and
- require conformance with regulations pertaining to Good Manufacturing Practices, records and reports, and inspections.[3,4]

Class I devices are regulated solely through general controls. The statute defined Class II devices as those devices that could not be designated as Class I but for which sufficient information existed to establish a "performance standard." Standards were visualized as a more stringent form of regulation; however, the FDA has promulgated no performance standards between 1976 and the present. Consequently, the Safe Medical Devices Act of 1990 provides for regulation under "special controls." In addition to potential regulation by performance standards, Class II devices are subject

to the general controls listed above, including Section 510(k) of the Food, Drug, and Cosmetic Act.

Section 510(k) requires that for any device brought to market after May 28, 1976—the date of enactment of the 1976 amendments—the sponsor must provide "premarket notification" to the FDA of its intent to market the device.* To be eligible for immediate marketing, the device must be judged by the FDA to be substantially equivalent to a device in use before that date. The FDA is required to rule on a 510(k) notification within 90 days of receiving it; if the agency does not respond, the company may proceed with marketing. If the FDA determines that a device is not substantially equivalent to one that has been marketed previously, it automatically places the device in Class III.

The pre-market approval (PMA) route for a Class III device is analogous to the NDAs and PLAs of drugs and biologics. The manufacturer must present data from "well controlled investigations" or other appropriate tests to provide "reasonable assurance" of the device's safety and effectiveness. Before the initiation of human clinical trials on a device, the Institutional Review Board (IRB) of the institution at which the trials are to be conducted must decide whether the device poses a "significant risk" to patients. If it does, the manufacturer must apply for an investigational device exemption (IDE) from the FDA in order to conduct the trial. If it does not, the FDA's permission is not required, and the manufacturer must only adhere to the sections of the IDE regulation that pertain to nonsignificant-risk devices.

AGENCY WORKLOAD AND ADVISORY COMMITTEES

The three centers vary in their workload for new product evaluations, with the CDER having the heaviest workload, the CDRH having the next heaviest, and the CBER having the lightest. Figures 3-1 and 3-2 indicate the budget and the total number of personnel for each center for fiscal year 1991.

A quantitative indication of the work of the three centers is presented in the following tables. Table 3-1 indicates the number and type of submissions or applications that were received by CDER for the years 1986

* Medical device manufacturers are required to submit a premarket notification if they intend to introduce a device into commercial distribution for the first time or to introduce, or reintroduce, a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected...." Premarket notification [510(k)] is not required for preamendment devices, devices under the IDE regulation, most transitional devices [devices previously regulated as drugs or antibiotics], and custom devices. In addition, a number of class I devices have been exempted by regulation from 510(k) requirements.

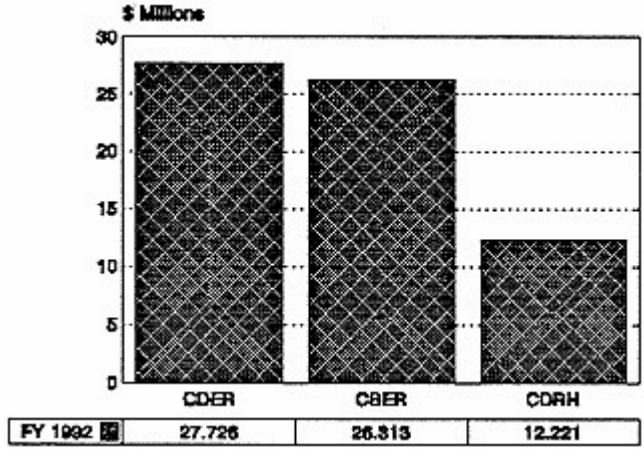


Figure 3-1 Fiscal year 1992 operating budgets for CDER, CBER, and CDRH.
Source: FDA/CDER/CBER/CDRH.

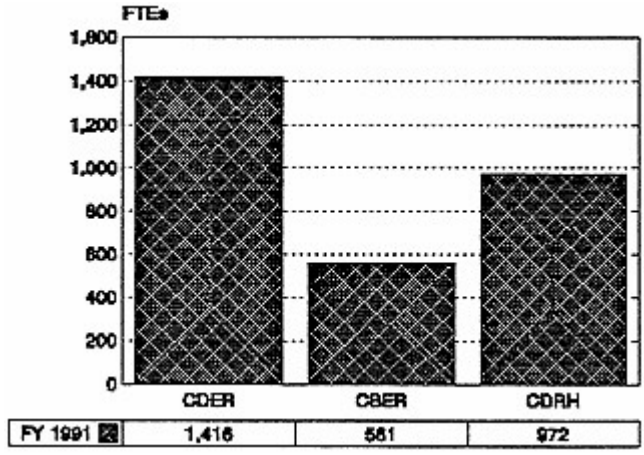


Figure 3-2 Allotment of full-time-equivalent positions in CDER, CBER, and CDRH.
Source: FDA/CDER/CBER/CDRH.

through 1991. Although the figure for original new drug applications (NDAs) fluctuates somewhat from year to year, in general, it reveals a steady pattern. Investigational new drug (IND) applications have reached the 2,000 level, of which nearly 20 percent are commercial.

Table 3-2 shows the same data on submissions to CBER for the years 1987 through 1991. Although the number of original product licensing applications (PLAs) fell back sharply in 1990 and 1991 from the three preceding years, it is expected that they will rise again as the biotechnology revolution generates an increasing number of new therapeutic products. This expected increase in demand can be seen in the doubling of original INDs from 1987 to 1991.

Table 3-3 reveals the level and nature of CDRH submissions. The number of original PMA applications appears relatively stable at fewer than 100 per year. However, the 510(k) applications have consistently run above 5,000 each year, indicating the high volume of medical device submissions that claim "substantial equivalence" to a pre-1976 device.

Table 3-4 indicates the stream of CDER approvals during the years 1986 through 1991. The criteria for "refusal to file" an application are currently being tightened up, and these figures may show an increase in the immediate future.

CBER approvals are shown in Table 3-5. The number of PLA approvals reveals a steady and significant increase during the five years from 1987 through 1991.

Table 3-6 shows a stable pattern for original PMA approvals for the 1987 through 1990 period. However, adding 1986 and 1991 to these data presents a picture of declining PMA approvals. Again, approvals of 510(k) applications run very high, consistent with the volume of such applications received. Approvals of IDEs (originals, amendments, and supplements) is stable and high.

Table 3-7 lists all standing FDA technical advisory committees as of July 1,1992.

Table 3-1 Submissions Received by the Center for Drug Evaluation and Research, Calendar Years 1986–1991

Submission Type	1986	1987	1988	1989	1990	1991
Original NDAs received	120	142	126	118	98	112
NDA resubmissions	18	24	30	33	16	12
Major amendments	344	286	408	455	474	435
NDA supplements	NA	1,889	1,857	1,867	2,006	1,670
Original ANDAs & AADA rec'd.	NA	NA	NA	784	312	311
Major amendments	NA	NA	NA	2,846	1,125	1,302
Original INDs	1,596	1,346	1,337	1,345	1,530	2,116
Commercial INDs	330	302	363	308	376	374

Note: NDA, new drug application; NA, not available; ANDA, abbreviated new drug application; AADA, abbreviated antibiotic new drug application; IND, investigational new drug.
Source: "Selected Calendar Year 1991 Information and Accomplishment Data," DHHS/PHS/FDA/CDER/OMB.

Table 3-2 Submissions Received by the Center for Biologics Evaluation and Research, Calendar Years 1987–1991

Submission Type	1987	1988	1989	1990	1991
Original PLAs	92	98	99	63	48
PLA amendment	379	421	445	458	552
Original ELAs	33	36	39	24	15
ELA amendment	93	162	198	192	148
Original INDs*	266	294	277	379	504

Note: PLA, product license agreement; ELA, establishment license agreement; IND, investigational new drug.

* INDs are reported by fiscal year.

Source: Center for Biologics Evaluation and Research/Office of Management.

Table 3-3 Submissions Received by the Center for Devices and Radiological Health, Fiscal Years 1986–1991

Submission Type	1986	1987	1988	1989	1990	1991
Original PMAs	69	81	96	84	79	75
PMA supplements	478	700	727	810	660	593
Original IDEs	206	218	268	241	252	213
IDE amendments	365	265	316	271	288	283
IDE supplements	2,884	2,836	3,391	3,038	3,043	3,647
510(k)s	5,063	5,265	5,536	7,022	5,831	5,770

Note: PMA, pre-market approval; IDE, investigational device exemption.
Source: "Office of Device Evaluation Annual Report(s) Fiscal Years 1986–91," DHHS/PHS/FDA/CDRH.

Table 3-4 Application Approvals by the Center for Drug Evaluation and Research, Calendar Years 1986–1991

Application Type	1986	1987	1998	1989	1990	1991
NDAs approved	98	69	67	87	64	63
NDAs approvable	71	39	31	48	41	46
NDAs refusal to file	14	22	17	10	14	23
NDAs not approvable	109	116	114	69	81	77
NDAs withdrawn	36	34	53	59	55	48
ANDA & AADA approvals	NA	NA	NA	265	80	193
ANDA & AADA not approvables	NA	NA	NA	1,899	828	1,080

Note: NDA, new drug application; ANDA, abbreviated new drug application; AADA, abbreviated antibiotic new drug application; NA, not available.
Source: "Selected Calendar Year 1991 Information and Accomplishment Data," DHHS/PHS/FDA/CDER/OMB.

Table 3-5 Application Approvals by the Center for Biologics Evaluation and Research, Calendar Years 1987–1991

Submission Type	1987	1988	1989	1990	1991
PLAs approved	33	44	52	70	60
PLAs withdrawn	6	19	14	19	17
PLAs inactive	3	2	4	0	0
PLAs denied	0	0	0	1	0
ELAs approved	15	16	24	29	19
ELAs withdrawn	2	4	4	5	5
ELAs inactive	2	2	2	0	0
ELAs denied	0	0	0	1	0

Note: PLA, product license agreement; ELA, establishment license agreement.
Source: CBER/OM.

Table 3-6 Application Approvals by the Center for Devices and Radiological Health, Fiscal Years 1986–1991

Submission Type	1986	1987	1988	1989	1990	1991
Original PMA	72	46	46	56	47	27
PMA supplement	477	565	652	519	700	479
Original IDE	213	224	260	245	248	220
IDE amendment	330	253	327	280	270	287
IDE supplement	3,599	2,784	3,405	3,023	2,968	3,705
510(k)s	5,359	4,992	5,513	6,136	6,197	5,367

Note: PMA, pre-market approval; IDE, investigational device exemption.
Source: "Office of Device Evaluation Annual Report(s), Fiscal Years 1986–91," DHHS/PHS/FDA/CDRH.

Table 3-7 FDA Standing Advisory Committees (as of July 1, 1992)

Center for Drug Evaluation and Research (CDER) Advisory Committees

Anesthetic and Life Support Drugs (5/1/78; 4/27/92)

Anti-Infective Drugs (10/7/80; 10/7/90; new charter in process)

Antiviral Drugs (2/15/89; 2/15/91; new charter in process)

Arthritis (4/5/74; 4/3/91)

Cardiovascular and Renal Drugs (8/27/70; 8/10/90; new charter in process)

Dermatologic Drugs (10/7/80; 10/7/90; new charter in process)

Drug Abuse (5/31/78; 4/27/92)

Endocrinologic and Metabolic Drugs (8/27/70; 8/21/90; new charter in process)

Fertility and Maternal Health Drugs (3/23/78; 3/29/92)

Gastrointestinal Drugs (3/3/78; 2/24/92)

Generic Drugs (1/22/90; 1/21/92)

Medical Imaging Drugs (2/24/92); previously Radio-pharmaceutical Drugs (8/30/67)

Oncologic Drugs (9/1/78; 8/8/90; new charter in process)

Over-the-Counter Drugs (8/27/91; new charter in process)

Peripheral and Central Nervous System Drugs (6/14/74; 6/4/92)

Psychopharmacologic Drugs (6/4/74; 6/4/92)

Pulmonary-Allergy Drugs (2/17/72; 5/22/92)

Center for Biologics Evaluation and Research (CBER) Advisory Committees

Allergenic Products (7/4/84; 7/9/90; new charter in process)

Biological Response Modifiers (10/28/88; 10/26/90; new charter in process)

Blood Products (5/13/80; 5/13/92)

Vaccines and Related Biological Products (12/31/79; 12/31/91)

Center for Devices and Radiologic Health (CDRH) Advisory Committees

Medical Devices (10/27/90)

Anesthesiology and Respiratory Therapy Devices Panel

Circulatory System Devices Panel

Clinical Chemistry and Clinical Toxicology Devices Panel

Center for Devices and Radiologic Health (CDRH) Advisory Committees

Dental Products Panel

Ear, Nose, and Throat Devices Panel

Gastroenterology-Urology Devices Panel

General and Plastic Surgery Devices Panel

General Hospital and Personal Use Devices Panel

Hematology and Pathology Devices Panel

Immunology Devices Panel

Microbiology Devices Panel

Neurological Devices Panel

Obstetrics-Gynecology Devices Panel

Ophthalmic Devices Panel

Orthopedic and Rehabilitation Devices Panel

Radiologic Devices Panel

Technical Electronic Product Radiation Safety Standards Committee (10/18/68)

Device Good Manufacturing Practice Advisory Committee (5/17/87)

Note: The dates in parentheses indicate the initial creation of a committee and its most recent reauthorization, which occurs every two years. Nearly all CDER and CBER advisory committees have been rechartered by the Commissioner following the chartering of a single CDRH Medical Devices Advisory Committee with 16 panels. If a committee has not yet been rechartered, reference is made to "new charter in process." Prior charters were signed by the Secretary; new charters are signed by the Commissioner.
Source: The Food and Drug Administration.

The nature and extent of use of advisory committees by the three centers are indicated in the following figures. Figure 3-3 indicates the total number of such committees, by center, from 1988 through 1991. For the three centers combined, there are nearly 40 committees.

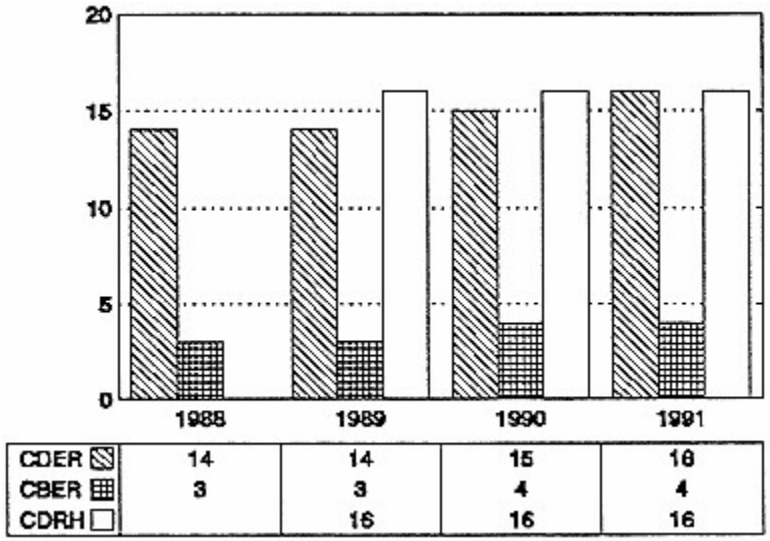
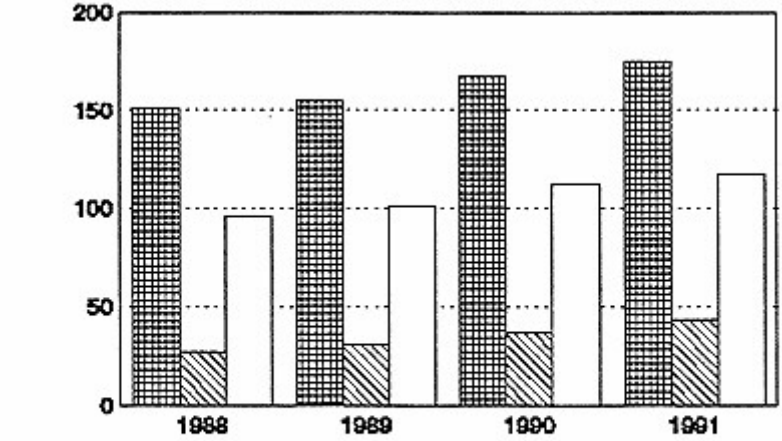


Figure 3-3 Number of advisory committees (and panels) for CDER, CBER, and CDRH.
Source: Annual Report, FDA/OC/OCM.

The total number of committee members serving on these committees is indicated in Figure 3-4. Over 300 individuals currently serve on the committees that advise the three centers. Both the number of committees and the number of members have remained relatively stable in recent years. However, the level of their activity has increased.

The increased number of advisory committee meetings is shown in Figure 3-5, which indicates more than a 50 percent increase from 1988 to 1991 for CDER, stability for CBER, and a decrease for CDRH.



	1988	1989	1990	1991
CDER	151	155	167	175
CBER	27	31	37	43
CDRH	96	101	112	117

Figure 3-4 Number of advisory committee members within CDER, CBER, and CDRH.
Source: Annual Report, FDA/OC/CMO.

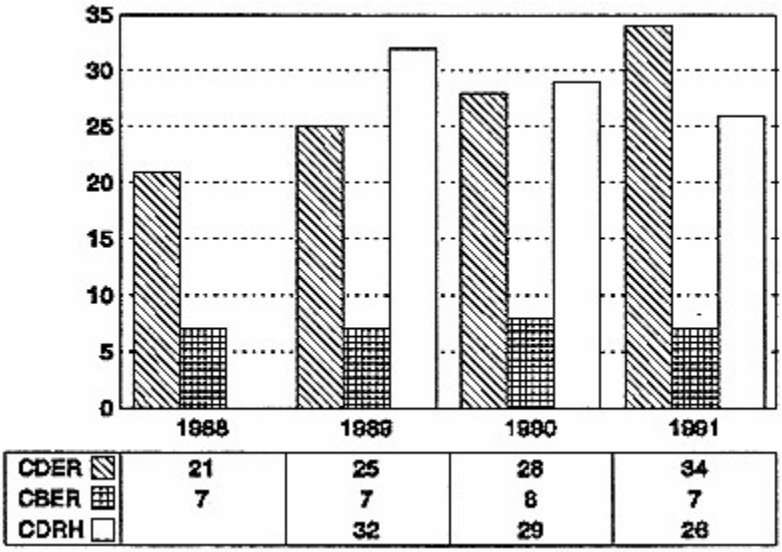


Figure 3-5 Number of advisory committee meetings per year for CDER, CBER, and CDRH.
Source: Annual Report, FDA/OC/CMO.

OFFICIAL PURPOSES OF ADVISORY COMMITTEES

The FDA established advisory committees to gain access to independent external expertise. Only in the case of medical devices were advisory committees required by Congress. This section describes the announced purposes of such FDA committees as outlined in the following FDA documents: the Code of Federal Regulations (CFR), the NDA Rewrite, the Medical Device Amendments of 1976, and the official committee charters.

The FDA Regulations

Although the FDA initiated its advisory committee system by internal administrative memoranda in the early 1960s, it did not codify the system's policies and procedures until the late 1970s. These policies and procedures appear today in the Code of Federal Regulations (CFR), Title 21, Part 14.*

Part 14 states the purposes of advisory committees in very general terms. The agency advocates their use when:

> the Commissioner concludes, as a matter of discretion, that it is in the public interest for a standing or ad hoc committee (*advisory committee* or *committee*) [emphasis in original] to hold a public hearing and to review and make recommendations on any matter before FDA and for interested persons to present information and views at an oral public hearing before the advisory committee.[5]

This chapter also discusses other provisions of Part 14 that pertain to the purposes of advisory committees in relation to committee charters.

The NDA Rewrite

The preamble to the 1985 FDA final rule on New Drug and Antibiotic Regulations contains a detailed statement of the purposes of advisory committees as applied to drugs.[6]** Known as the NDA Rewrite, this rule

* All FDA regulations are codified in Title 21 of the Code of Federal Regulations. Part 14, "Public Hearing Before a Public Advisory Committee," deals with general provisions, meeting procedures, establishment of advisory committees, records of meetings and hearings before advisory committees, members of advisory committees, standing advisory committees, the Technical Electronic Products Radiation Safety Standards Committee, color additive advisory committees, and advisory committees for human prescription drugs.

** At this time, the two bureaus on drugs and biologics were merged.

was the first phase of Reagan administration efforts to improve the efficiency of the drug evaluation process. Although the proposed rulen[7] had not dealt with the role of outside experts in the new drug evaluation process, the FDA received enough comments on this matter that it decided to use the preamble to the final rule as a way to set forth "FDA policy in this area."

In the preamble to the NDA Rewrite, the FDA agreed that the use of outside experts "adds to the quality and credibility of the decision making process." The agency stated its belief that "the primary goal of the advisory committee (and outside consultant) system should be to help the agency make sound decisions based upon the reasoned application of good science." It indicated that the agency used advisory committees to bring outside experts into the new drug evaluation process for two main reasons: (1) to supplement the agency's internal expertise and (2) to help the agency staff stay current with "state-of-the art technology" by encouraging close working relationships between the staff and outside experts. Advisory committee meetings, it also noted, "serve an important function by providing a public forum for discussion of issues."

The preamble also stated that advisory committees "generally" advise the Commissioner on the "safety and effectiveness and regulatory control of human prescription drugs," including "whether the available information is adequate to support a determination that a particular drug meets the statutory standards for proof of safety and effectiveness necessary for marketing approval." At the FDA's request, such committees review "certain critical studies or critical elements of studies on drug products under consideration and labeling issues"; they also respond to specific FDA questions that ask them to identify "the adequate and well-controlled studies which demonstrate effectiveness, the seriousness of certain adverse effects, and whether additional studies or data are necessary before a decision can be reached."

The FDA identified the following as high-priority items on which it sought advice from advisory committees:

> drugs subject to active IND's and pending NDA's that offer potential therapeutic advances, that pose significant safety hazards, that present narrow benefit/risk considerations, that have novel delivery systems or formulations, that are the subject of a major scientific or public controversy, or that are the subject of special regulatory requirements, such as a limitation on clinical trials, a patient follow-up requirement, postmarketing studies, or boxed warnings.

The agency also indicated that it sought advice on broader clinical research issues and had developed approximately 25 clinical research

guidelines with the help of advisory committees, professional societies, and consultants to the drug industry. These guidelines consisted of "generally accepted principles for reaching valid conclusions about the safety and effectiveness of drugs, and [the] views of recognized experts about appropriate methods for studying specific classes of drugs."

The preamble also noted that FDA used *individual* advisory committee members as consultants in several ways. For example, the FDA included them in meetings with sponsors to discuss specific scientific issues, to participate in "end-of-Phase II" conferences that helped to plan Phase III studies (as noted in the "IND Rewrite proposal"),[8] and on an ad hoc basis as technical consultants or expert reviewers, especially in cases in which the agency lacked resources or expertise.

"In summary," the preamble stated, "FDA believes that the primary goal of the advisory committee (and outside consultant) system should be to help the agency make sound decisions based upon the reasoned application of good science."

Medical Device Statutes

In the case of medical devices, the law requires the use of advisory committees. The Radiation Control Act of 1968, which amended the Public Health Service Act, directed the Secretary to establish a Technical Electronic Product Radiation Safety Standards Committee (TEPRSSC) "to provide consultation before the Commissioner prescribes any performance standards for an electronic product." In advising the Commissioner, the TEPRSSC may propose standards for his consideration, consult on standards he has proposed, and recommend action on "any other matter" related to the act. Authority to act on the advice of the TEPRSSC is explicitly vested in the Commissioner. The FDA has always administered this provision of the law, currently through the CDRH, and it is the first instance of the agency being required by statute to establish and maintain an advisory committee.

The Medical Device Amendments of 1976 directed the Secretary to use advisory committees in two ways. First, they directed him to establish "panels of experts" for classifying medical devices intended for human use "according to the various fields of clinical medicine and fundamental science" in which these devices were to be used. Second, they required him to establish advisory committees (other than classification panels) to review proposed regulations for medical device performance standards, to review all PMA applications, and to make recommendations on Good Manufacturing Practice regulations. For the purposes of this study, the use of advisory committees for premarketing approval is the most important concern.

FDA Advisory Committee Charters

The charters of specific FDA advisory committees indicate that their purpose is to advise the Commissioner on the safety and effectiveness of the product in question. The typical CDER advisory committee charter reads as follows:

> [The committee] reviews and evaluates available data concerning the safety and effectiveness of marketed and investigational human drug products for use in [specified disease treatments] ... and makes appropriate recommendations to the Secretary, the Assistant Secretary, and the Commissioner of Food and Drugs.

The charges of two CDER committees are couched in slightly different language. The Generic Drugs Advisory Committee is to advise on the safety and effectiveness of human generic drug products for use in treating "a broad spectrum of human diseases." The Drug Abuse Advisory Committee, with a broad charge, advises the FDA Commissioner on "the scientific and medical evaluation of all information gathered by the Department of Health and Human Services and the Department of Justice with regard to safety, efficacy, and abuse potential of drugs or other substances and recommends actions to be taken by the Department of Health and Human Services with regard to marketing, investigation, and control of such drugs or other substances."

The charters of the four CBER advisory committees also focus on the evaluation of data related to safety and effectiveness. In addition, the charges to the Biological Response Modifiers Advisory Committee and the Vaccines and Related Biological Products Advisory Committee require them to consider "appropriate use," and those to the Allergenic Products Advisory Committee and the Blood and Blood Products Advisory Committee to consider labeling issues.[*] Yet the scope of CBER advisory committees extends beyond these functions in one important respect, in which they differ from CDER and CDRH committees. With its origins in the biologics program of the NIH, the CBER also uses its advisory committees to review the quality and relevance of the center's intramural research program, which provides scientific support to its product regulation responsibilities, and the quality and performance of its research personnel.

[*] The Blood and Blood Products Advisory Committee also functions as a device advisory committee for blood-related devices, examining issues related to classification, safety and effectiveness, formulation of product development protocols, review of PMAs, and the "reclassification, exemption, and banning of devices."

The CDRH, as noted in Chapter 2, used advisory panels to classify pre-1976 medical devices into one of three risk-related categories; it terminated these classification panels once their responsibilities had been carried out. The center also used approximately 16 separately chartered advisory committees for product evaluation purposes. In 1990, the CDRH formally terminated its existing advisory committees, established a single Medical Devices Advisory Committee, and reconstituted the previous committees as 16 "panels" of the new committee. The center did so to enable it to bring needed expertise to bear on a given product review and to meet the requirement for a quorum of voting members more easily. The single committee consists of a maximum of 148 members, of whom 114 are standing voting members and 34 are nonvoting members (16 consumer representatives and 18 industry representatives); the members are distributed to panels as before.

Under this arrangement, the device panels function as they did before as committees, except that the responsible FDA official can invite committee members from other panels, as well as designated consultants, to serve as voting panel members at a particular meeting. This can occur under two circumstances: first, "when expertise is required that is not available among the current voting standing members of the panel," and second, to meet the need for a quorum when one is lacking.[9]

The CDRH describes the purposes of its rechartered advisory committee structure as follows:

> Reviews and evaluates available data concerning the safety and effectiveness of [specified devices] currently in use and advises the Commissioner regarding recommended classification of these devices into one of three regulatory categories; recommends the assignment of a priority for the application of regulatory requirements for devices classified in the standards or premarket approval category; reviews classification of devices to recommend changes in classification as appropriate; recommends exemption of certain devices from the applications of portions of the Act; advises on the necessity to ban a device; and responds to requests from the Agency to review and make recommendations on specific issues or problems concerning the safety and effectiveness of devices.

Some variation exists within the CDRH panels. For example, the Dental Products Panel functions at times as a nonprescription drug advisory panel. In addition, the Radiologic Devices Panel is to advise on "a coordinated program" for the medical application of radiation that maximizes diagnostic information and therapeutic benefits per unit of exposure.

About the same time that this rechartering occurred, Congress enacted the Safe Medical Devices Act of 1990.[10] Section 16 of that act required that regulations be issued to determine the primary mode of action of a product that combined a drug, device, or biological product and to assign primary jurisdiction to the responsible FDA center. The FDA, in implementing this requirement, expanded it to include all product jurisdiction issues. The results of this were new regulations; three new intercenter agreements, and the rechartering of CDER and CBER advisory committees to permit the use, when expertise is needed or a quorum is lacking, of any FDA technical advisory committee member (and designated consultants) as a voting member on any other committee. The implications of this rechartering are discussed in Chapter 7.

The CDRH has two committees that are not engaged in product evaluation. The Device Good Manufacturing Practice Advisory Committee is responsible for reviewing proposed regulations for "good manufacturing practices governing the methods used in, and the facilities and controls used for, the manufacture, packing, storage, and installation of devices, and . . . the feasibility and reasonableness of those proposed regulations." The TEPRSSC, as mentioned earlier, advises the Commissioner "on the technical feasibility and reasonableness of performance standards" to control radiation emission from electronic products.

THE USES OF ADVISORY COMMITTEES

The above discussion indicates the range of official purposes of FDA advisory committees in the area of drugs, biologics, and medical devices. Not surprisingly, then, the agency—or, more accurately, its program units—uses such committees in a number of different ways. These variations derive from the following sources:

- the three separate centers—their histories, technical and regulatory responsibilities, workloads, and their organizational "cultures";
- the stage of product development and evaluation—prelicensing, licensing, postmarketing approval;
- the means by which the centers seek external advice—advisory committees, Special Government Employee (SGE) consultants, primary reviewers, and workshops; and
- other factors.

The "other factors" may comprise: the class of therapeutic products under consideration; the stage of scientific development of the pertinent clinical field or area; the specific tasks of a given advisory committee; the different

reviewing divisions, including the relationship between the review organizations and the advisory committees; the personalities of different review officials; and the absence of sustained FDA-wide policy guidance. How these factors interact to affect variation in the use of advisory committees can be addressed by taking each center in turn.

Variations Among Centers

The CDER, which is the oldest FDA user of advisory committees and the center with the most complicated history of use, brought them into existence in the decade following the 1962 drug amendments. That legislation required that, in addition to safety, the effectiveness of drugs be established for all old drugs—prescription and over the counter—marketed between 1938 and 1962 on the basis of safety alone; all new drugs were to be evaluated for both safety and effectiveness as well. The agency thus had both an immediate need, to acquire expertise that it did not have on its staff, and a long-term need, to recruit personnel with greater medical and scientific expertise than it then had. The legislation also reinforced the adversarial relationship between the agency and the regulated industry. Not surprisingly, among the three centers considered in this report, agency-industry relations have been most confrontational for drugs.

The CDER advisory committee system that developed is organized along the lines of therapeutic agents or product lines, from an industry perspective, as indicated in Table 3-7. This organization parallels the drug evaluation units of the center—the two Offices of Drug Evaluation and their respective divisions, the Pilot Drug Evaluation Office, the Office of Generic Drugs, and the Office of Over-the-Counter Drugs.

In biologics, vaccine development has been justified by a public health rationale and embedded in a public health institutional framework. The need for government regulation of safety is not subject to dispute. The economic incentives for commercial vaccine developers have been weaker historically than for drug manufacturers, and agency-industry relations are less confrontational than for drugs.

The CBER advisory committee system is organized according to therapeutic categories or product lines, as Table 3-7 makes clear. The reviewing offices of the CBER, however, do not correspond directly to the advisory committee structure. Instead, several units may review a given PLA, depending on the biologic under consideration.

The CBER system, unlike those of the CDER and CDRH, extends beyond product evaluation to the review by the four advisory committees of CBER intramural research programs and research personnel. One question raised by this practice is whether four advisory committees, each reviewing

a portion of the intramural research program, fragment the oversight of that effort. It is possible that a single "board of scientific counsellors," charged with reviewing all CBER intramural research, might be a more appropriate structure.

Many observers have viewed the CDRH's implementation of the 1976 amendments as sensitive to the needs as to the device industry and favorable to product innovation, of well as to the physicians and other health professionals who use the devices. Although the Safe Medical Devices Act of 1990 imposed a number of new requirements on the FDA that may affect its relations with manufacturers, it gave the agency greater discretion in the use of advisory committees, as noted earlier.

The CDRH advisory committee system, like the CDER system, is organized along the lines of therapeutic agents or product lines. Internal organization of the Office of Device Evaluation parallels these advisory committees. One feature that differs between the CDRH and CDER, however, is that executive secretaries and division directors play different roles in product evaluation. The CDRH executive secretary is typically a medical review officer to whom additional executive secretarial functions have been assigned, whereas the division director may be mainly a manager.

A major tension in the CDRH system, not found in those of the CDER and CBER, is that advisory committees have been the primary means to obtain expert clinical advice for product reviews that are conducted by a professional staff composed predominantly of engineers. Consequently, CDRH usually designates one member of an advisory committee as a "primary reviewer" for each PMA that comes before it, and the committee member receives additional compensation for such work.[*]

Center Workload and Stage of Advisory Committee Use

The CDER workload of INDs, NDAs, and other applications is the greatest of any of the three centers, as reflected in Tables 3-1 through 3-4. This workload has led the CDER to focus its use of advisory committees on issues that arise in the product evaluation stage, rather than on earlier or later stages. The evaluation stage involves (1) review of specific NDAs and (2) consideration of scientific and technical policy issues related to the review of a class of products. Although the CDER devotes some committee time to the preapproval (e.g., clinical trial) and postmarketing stages of drug

[*] FDA regulations authorize payment to advisory committee members for homework on an hourly basis for assignments that require "a definitive study" and "tangible end product," such as a written report, provided that this end product does not represent the end product of the advisory committee [21 CFR Part 14.95(c)]. See "Compensation" in Chapter 8.

development, the CBER, in contrast, is involved earlier, more deeply, and on a more sustained basis with the development of a specific biologic, such as a vaccine, in part because of its lower volume of work.

Until recently, the CBER has had the smallest workload of the three centers. Coupled with the public health character of its purview and its less confrontational relationship with industry, this has meant that the CBER has been involved in product development and evaluation earlier and more extensively than is true for either drugs or devices. Consequently, CBER advisory committees also have been engaged in the evaluation of biologics at earlier stages than is usual for drugs.

The biotechnology revolution, however, is generating an increasing stream of new therapeutic biological products. This trend has led the FDA to increase the number of professional medical and scientific personnel on its staff. New biological therapeutics now drive the growth occurring in the CBER's work, the impact of which is felt largely by the Biological Response Modifiers Advisory Committee. As these developments unfold in the coming decade, the CBER workload will continue to increase, and the pressures of scarce professional personnel resources may impel the center to focus more on the licensing, rather than the prelicensing, stage.

The CDRH workload is complicated; unlike drugs and biologics, it is based on risk-related classification of devices. For Class II medical devices, the FDA must determine whether a device is the substantial equivalent of one marketed before the 1976 amendments. As described earlier, some Class III devices have been on the market since before 1976, while others have reached the market since then through the 510(k) procedure and still others by the PMA route. The PMA workload that advisory committees now face is substantial and growing; rechartering of multiple advisory committees into a single committee with multiple panels presumably has made this workload easier to manage.

The law requires the sponsor of a Class III device marketed before the 1976 amendments to submit a PMA application when the agency calls for safety and effectiveness data on all devices in that category. The Safe Medical Device Amendments of 1990 required the FDA, by December 1, 1995, to call for PMAs or to reclassify as Class II approximately 130 such devices. Although the agency claims that it lacks the resources to fulfill this statutory requirement completely, it is calling for PMA applications for some of these devices. It is likely that the resulting PMAs will be reviewed by advisory panels. For example, the two meetings of the General and Plastic Surgery Advisory Panel that considered the safety and effectiveness of silicone gel breast implants in November 1991 and February 1992 were reviewing one of these pre-1976 devices.

Other Means of Seeking Advice

In addition to the use of advisory committees, the three centers formally seek external expert advice through Special Government Employee (SGE) consultants and workshops.

Consultants: The FDA appoints all voting members of its technical advisory committees as Special Government Employees to permit them to be paid and reimbursed for expenses. All FDA consultants are also SGEs, but not all SGE consultants are advisory committee members. Conversely, a scientist can be both a consultant and a committee member. The SGE status is mainly used to pay or reimburse scientific expertise.

The CDER uses consultants, some of whom are advisory committee members and some of whom are not, throughout the drug evaluation process. For example, it may bring an advisory committee member, as a consultant, into an "End of Phase II Conference" with a drug sponsor. Or it may use an SGE consultant who is not an advisory committee member for that purpose. The FDA may also use a nonmember SGE consultant as a consultant to an advisory committee. All three centers use consultants in these various ways.

In some situations, the CDER may draw on the expertise of consultants who have been engaged by product sponsors. If the FDA has a problem with a sponsor's application, the agency may ask the firm to come to a meeting to discuss the problem and to bring with it one or several of its principal consultants. The agency thus may extend its access to external expertise, when it deems it useful, to consultants to the industry.

Formal Workshops: The three centers differ in the extent of their use of workshops. The CDER often uses this approach, describing a meeting as a minisymposium and organizing it in conjunction with an advisory committee. An example of this kind of activity was a one-day meeting on dose-response measurement of angiotensin-converting enzyme inhibitors that was organized by the Cardiovascular and Renal Drugs Division. The second day was a formal Cardio-Renal Drugs Advisory Committee meeting, focused on specific submissions.

Perhaps because of the public health linkage with vaccine development, the CBER sponsors or cosponsors a number of workshops each year devoted to scientific issues that bear on its regulatory responsibilities. The distinctions between an advisory committee meeting and a workshop are several: workshops are generally called to explore the state of the science in relation to a given issue and not to advise the FDA; the workshops, including all technical presentations, are open to the public, especially the relevant

technical community, without regard to organizational affiliation or conflict of interest; and workshops are not governed by the Federal Advisory Committee Act.*[11]

A central question about consultants and workshops is whether either of these mechanisms provides value equivalent to that of advisory committees? If so, in what contexts? The FDA wants to be able to say of advisory committees, "We assembled the best people in the country; they heard the evidence, debated its implications, and provided us with this advice." Consultants may provide detailed advice of great value on specific matters; however, their role does not provide a forum for public discussion, nor do they perform in a fashion that allows the FDA to make the above claim to the public and press. On the one hand, workshops allow the agency to generate a synthesis of the state of scientific development in an area. On the other hand, because they may not result in advice, workshops are unable to perform certain roles that advisory committees fulfill. The issue may be whether these other mechanisms are genuine alternatives to advisory committees or are more appropriately understood as adjuncts to them.

Another question is whether these other methods for tapping the expertise of outside scientists escape the strictures of the Federal Advisory Committee Act? In this context, the conflict-of-interest restrictions do apply to agency consultants, but the regulations allow "two or more FDA consultants" to meet with the agency on an ad hoc basis.[12]

SUMMARY

The FDA advisory committee system has been an integral part of the product evaluation process for drugs, biologics, and medical devices. The agency has made increasing use of these committees over time.

Procedures for using advisory committees vary from center to center and often within centers. These variations have many explanations, some quite clearly justifiable in operational terms but others seemingly the product of neglect by the agency's central administration or the idiosyncratic preferences of agency officials directly responsible for their ongoing management. For much of the past decade, little attention appears to have been devoted to establishing and maintaining an optimum level of agency-wide uniformity in committee procedure and management.

* An example of a CBER-related workshop was a two-day meeting organized by the Institute of Medicine's Forum on Drug Development on the "microheterogeneity of biological macromolecules." The workshop considered the scientific issues underlying small changes in large biological molecules and the implications of these issues for FDA policies.

The primary purpose of FDA advisory committees, as stated in the NDA Rewrite, is to assist the agency in making "sound decisions based upon the reasoned application of good science." They do so by advising on the approvability of specific product applications based on an examination of the adequacy of the data supporting claims of safety and effectiveness. In addition, advisory committees provide technical advice on broader issues relating to product evaluation generally.

Advisory committees are not the only ways by which FDA seeks external expert advice. The agency also makes use of consultants and workshops. These other mechanisms are best viewed as complementary to rather than alternatives to advisory committees. They reflect a natural response by a regulatory agency that depends on access to expert scientific and clinical information to fulfill its statutory responsibilities.

The IOM committee was very conscious that the use of advisory committees by the FDA was embedded in this broader context of seeking and obtaining external expert advice. It has focused almost exclusively on the use of these technical advisory committees, however, because, by common judgment, that is the component currently most in need of attention.

NOTES

1. Food and Drug Administration, *New Drug Development in the United States* (Rockville, Md.: Food and Drug Administration, January 1988).
2. Pharmaceutical Manufacturers Association, *In Development: Biotechnology Medicines* (Washington, D.C.: Pharmaceutical Manufacturers Association, 1991).
3. Food and Drug Administration, *Everything You Always Wanted to Know About the Medical Device Amendments and Weren't Afraid to Ask* , HHS Pub. FDA 90-4173, 3rd ed. (Washington, D.C., August 1990).
4. Ibid., pp. 12 and 15.
5. 21 CFR 14.1(a)(1), 1991.
6. 50 FR 7452, February 22, 1986.
7. 47 FR 46622, October 19,1982.
8. 48 FR 26732, June 9, 1983.

9. Food and Drug Administration, "Charter, Medical Devices Advisory Committee," (Washington, D.C., October 27, 1990).
10. Public Law 101-629, November 28,1990.
11. Institute of Medicine, *Microheterogeneity of Biological Macromolecules: Report of a Workshop* (Washington, D.C., 1991).
12. 21 CFR 14.1(b)(5)(ii).

4

Recurring Issues

Although technical advisory committees have been an important part of Food and Drug Administration operations for more than two decades, a number of issues about their use have been the focus of recurring controversy. This chapter examines these issues through the lens of prior reports on the FDA that have dealt in some important way with advisory committees.

One cluster of issues involves the purposes, roles, and functions of advisory committees. Views on these issues appear to vary as a function of the observer—FDA leadership, FDA middle managers, academic medical scientists, industry spokesmen, and consumer representatives. A second set of issues, more prominent in the 1970s than today, reflect the suspicion of a populist Congress, which has sometimes seen scientific experts as too closely allied with the regulated industry—or at least as too inclined to endorse new technologies at the expense of risk to patients. Third, the issue of the independence of advisory committees, mainly from influence by the agency, but also from product sponsors, has long persisted as a topic.

The discussion that follows examines these major issues and more detailed questions about committee operations and management. The chapter also describes the "goldfish bowl" within which the FDA and its advisory committees operate.

MAJOR PRIOR REPORTS

The history of the FDA is a history of reports about the FDA, as Hutt has noted.[1] In this section, we review several reports that have dealt with FDA advisory committees, usually in the context of reform of the drug approval process: the Fountain Committee report of 1976, the Dorsen Committee report of 1977, the McMahon Commission report of 1982, and the Lasagna Committee report of 1990. This brief historical review makes clear that many of the issues surrounding FDA advisory committees that are

addressed in this report have been considered before, raising questions about what is required to maintain a system that has broad public acceptance, is well administered and adequately funded, and contributes to the public health of the country.

The Fountain Committee Report (1976)

In 1976, the House Committee on Government Operations issued a report, *Use of Advisory Committees by the Food and Drug Administration*,[2] following hearings in 1974 and 1975 before its Subcommittee on Intergovernmental Relations and Human Resources. Ile subcommittee critically reviewed the use of advisory committees by the FDA's Bureau of Drugs in the light of the 1972 Federal Advisory Committee Act (FACA), over which the full committee had jurisdiction.*

The FACA had imposed four requirements for establishing an advisory committee: (1) a formal process should be used to determine the need for a committee; (2) membership should be "fairly balanced" as well as technically expert; (3) meetings should be conducted according to procedures of advance notice and a quorum requirement, and should be open to the public; and (4) detailed minutes and transcripts should be maintained as the meeting record.[3]

The Fountain Committee report, concurring with a major goal of Congress in enacting the FACA that agencies should "limit the number of advisory committees to the minimum necessary" (p. 3), recommended that the FDA reduce the number of advisory committees to those having a clear justification, limit the frequency of their meetings, and eliminate all nonessential uses. The report emphasized improved management and compliance with the act—FDA staff and advisory committee members should adhere to its standards, and Congress should monitor the agency to prevent inadequate fiscal and management oversight of committees. It recommended that the FDA remedy a perceived lack of balance in the composition of advisory committees, that it cease to close meetings improperly, that meetings not be held in places that discouraged public attendance, that complete minutes of meetings be kept, and that verbatim transcripts not be destroyed prematurely.

Several recommendations sought to strengthen advisory committees and their independence from the FDA. The report recommended that the FDA

* The subcommittee was chaired by Representative L H. Fountain (D., N.C.). Hutt indicates that Rep. Fountain held hearings (as many as three or four a year) on all aspects of the FDA from 1964 until he retired from Congress in 1982. His successor as subcommittee chairman, Rep. Theodore Weiss (D., N.Y.), continued that tradition until his death in September 1992.

take steps "to assure that advisory committees are properly instructed and provided adequate time and information for thorough and appropriate scientific analysis and review," that committees be permitted "to arrive at independent scientific findings without further intervention by FDA to influence their judgment on the basis of non-scientific considerations," and that the FDA end the practice of "seeking recommendations from advisory committees on matters that have already been decided, or in order to bypass critical staff review of the data submitted in new drug applications."

On the other hand, the subcommittee deplored undue reliance on advisory committees by the agency. It recommended that the FDA rely primarily on its own staff to carry out its responsibilities and use advisory committees only in exceptional circumstances involving difficult medical or scientific issues for which outside expertise was clearly required. The FDA was also enjoined to utilize its full-time professionals more effectively and, where necessary, to upgrade its medical, scientific, and technical personnel through advanced training, participation in scientific research, and similar professional development activities.

The Fountain Committee report reveals congressional suspicion about the FDA's use of advisory committees and a suspicion that expert committees were being used to reinforce closed decision-making processes that favored industry views. Hence, its recommendation that the FDA strengthen its own professional staff and avoid becoming overly dependent on outside committees. In fact, the report emphasized the technical capabilities of the FDA staff and argued that these staff could handle some, if not most, of the agency's technical decisions.

Echoes of the debate about internal staff competence versus external expertise are still heard today. Although the FDA staff, in the period immediately after the 1962 amendments, typically lacked the technical competence to evaluate drugs for effectiveness as well as safety, the agency long ago upgraded the quality of its professionals. Today, the issue of staff versus outside experts takes two forms: some observers see advisory committees as a partial counterweight to cautious, risk-averse government regulators; others see them as a necessary means by which the FDA staff stays abreast of the frontiers of science and clinical medicine.

The Dorsen Committee Report (1977)

In early 1975, as the Fountain Committee was holding its first hearings on FDA advisory committees, the Department of Health, Education, and Welfare (DHEW) established the DHEW Review Panel on New Drug Regulation to examine FDA policies and procedures related to the approval and disapproval of new drugs. Chaired by Norman Dorsen, professor of law

at New York University, the panel's final report[*4] declared that the system of new drug regulation was fundamentally sound but needed substantial improvement.

The report identified four shortcomings that needed remedying. First, the regulatory system of the Bureau of Drugs was unnecessarily closed to public review and participation, and overly dependent on informal, unreviewable communications between the FDA and drug companies. Second, the scientific capacity of the agency was inadequate and, unless corrected, likely to deteriorate further. Third, the bureau employed unacceptably imprecise standards and unstructured, inefficient procedures for reviewing new drug applications. Fourth, the agency had not devoted enough attention to approved drugs (pp. 106–107).

In the context of these criticisms, a panel of the full committee made a number of recommendations regarding the advisory committees of the Bureau of Drugs. In general, it called on the FDA to clarify its policies and procedures to ensure the uniform use and functioning of advisory committees among divisions. Regarding advisory committee members, the panel recommended that the FDA should issue written guidelines for selecting members; DHEW should abolish its policy barring concurrent membership on more than one departmental committee; should establish a "committee on committees" to recommend nomination procedures; should rescind existing regulations concerning consumer representation and provide for voting public interest members on all standing committees.

On financial conflict of interest, the Dorsen committee recommended that rules and procedures should be strict enough to guarantee the integrity of advisory committees but flexible enough to allow the FDA to attract and retain qualified members; the agency should use specific rules to disqualify members with serious conflicts but apply graduated restrictions to different degrees of conflict; all committee meetings should be public, all significant potential conflicts of interest should be fully disclosed; committees should be restricted to advising on narrow scientific questions rather than broad regulatory matters; and efforts should be increased to find qualified candidates with fewer potential conflicts.

Advisory committees, the report recommended, should be involved in reviewing both investigational new drugs (INDs) and new drug applications (NDAs). The FDA should provide all advisory committees a list of INDs and NDAs currently under review by their respective drug groups; the agency should use members to review significant INDs; the FDA should

[*] The committee had issued two interim reports in April 1977: "The Use of Standing Advisory Committees by the Bureau of Drugs of FDA" and "Conflicts of Interest on Standing Advisory Committees of the Bureau of Drugs, FDA."

document its decision to refer an IND or NDA to a committee; and an committees should adopt the practice of assigning individual members as primary reviewers of INDs and NDAs.

Recommendations dealing with committee operations included the following: the FDA should continue its efforts to send materials to advisory committee members at least three weeks before a meeting; sponsoring companies should receive the questions sent by FDA to the committee; and the Bureau of Drugs should adopt a policy against industry communicating directly to advisory committee members. In addition, the FDA should ask advisory committees precise questions about those matters on which it wished assistance and refrain from asking about evidence of safety and efficacy; FDA staff, in presentations to a committee, should refrain from stating their own views about the advice the committee should offer; draft minutes should be distributed to members as soon as they are written; and the FDA should periodically inform its committee members of the status of their recommendations. It also recommended that the FDA should limit the criteria for removal of an advisory committee member to behavior so disruptive that it significantly impedes the proper functioning of the committee; the agency should ensure that members do not discuss committee business in private; and committee members should refrain from discussing nonscientific issues such as economic or malpractice questions at meetings.

The panel report recommended that the handbook under preparation for orienting advisory committee members should include the relevant FDA statutes, the regulations for new drug approval (including the standards of safety and effectiveness) and for advisory committees, a description of the matters FDA will refer to committees, and a statement of how FDA hopes to use committee members as reviewers of INDs and NDAs.

Recommendations of the Dorsen Report to expand the scope of advisory committee responsibilities also find expression in the McMahon and Lasagna reports (see the later discussions). Suggestions that committees guide sponsors in the early stages of product development, especially the design and conduct of clinical trials are seldom accompanied by detailed supporting analysis. The agency has predictably resisted such expansion, noting that it would require greater agency resources and would increase committee workloads substantially. In general, the FDA prefers to focus more on using committees for product evaluation and for assessing broad issues of drug, biologic, or device evaluation.*

* As noted in prior chapters, the Center for Biologics Evaluation and Research involves itself and its advisory committees more deeply than the other centers in early stages of product development, a pattern derived from its history and regulatory responsibilities.

The McMahon Commission Report (1982)

In 1981, at the initiative of Representatives Scheuer and Gore, Congress authorized the creation of a Commission on the Federal Drug Approval Process (known as the McMahon Commission, after its chairman). The Commission reported in March 1982 on "changes that would enhance the speed and quality of the approval process while maintaining the existing level of protection of the public health"[5] (p. 2). Its report focused on four questions: the scientific evidence needed to conclude that a drug was safe and effective and who should assess the sufficiency and meaning of the evidence; the documentation needed by the FDA to support marketing or testing and the timing of its submission; the most efficient use of FDA resources to perform the agency's duties in the IND and NDA processes; and the "style of interaction" between the FDA and the pharmaceutical industry most appropriate to ensure efficiency and quality in the drug review process.

The McMahon Commission proposed the following reforms: outside review boards should be used in the approval process; new indications for approved drugs should be completely exempt from IND requirements; a streamlined approval process for generic drugs should be established; and manufacturers should no longer be required to send raw data to the FDA. The report was optimistic about speeding the drug approval process, although a minority report commented that it failed to recognize the substantial progress FDA had made in this regard.

Among its recommendations, the commission called for greater use of outside experts in the approval process: review procedures should be revised "to afford a more significant role" to experts from the academic and government biomedical research communities, and "due weight" should be given to the judgment of clinical investigators as to whether the standard of effectiveness had been met. It also proposed that outside experts should "become more actively involved," at the request of the FDA or a drug sponsor, in planning clinical trials, advising on INDs or new indications of an approved drug, and reviewing of NDAs.

The McMahon commission further recommended that the Commissioner seek the help of "leading professional societies, universities, and other appropriate bodies" in obtaining the "most qualified experts in various fields of pharmacology and therapeutics" as consultants and advisory committee members. It agreed with the Dorsen report's proposal for a "committee on committees" to broaden the selection of advisory committee members.

Regarding conflict of interest, the commission recommended that the FDA commissioner request from the Department of Justice "a less restrictive interpretation" of the federal conflict-of-interest statute than that issued in

1978, reflecting its belief that greater use of experts, as consultants and advisory committee members, could reduce the time needed for review (pp. 78–82). With a less conservative interpretation, it argued, "more experts could participate, and thus they could be involved earlier and more continuously in the course of developing important new drugs, [which] could . . . avert clinical studies that are not needed for NDA approval, expedite review of research data, and enhance the quality of FDA decision making" (p. 3).

The McMahon Commission report reflected an optimistic view that greater use of advisory committees would shorten the drug approval process. This view, which reappears over time, assumes that advisory committees can substitute for agency personnel. Advocacy, again, draws little support from analysis. The FDA tends to respond that greater use of advisory committees requires more, not fewer, agency staff.

The Lasagna Committee Report (1990)

The National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, chaired by Dr. Louis Lasagna, was created in late 1988 by the President's Cancer Panel, in response to a June request of then-Vice President George Bush. Its report, issued in August 1990, made a number of recommendations about the drug development and evaluation process.[6]

The Lasagna Committee report made several recommendations regarding advisory committees. It first recommended that a standing policy and oversight committee be established by the Secretary of Health and Human Services. This committee, which would report to the Secretary, would "monitor the Food and Drug Administration's needs and performance with regard to the regulation of drugs and biologics for human use."

The report also called for "a fundamental restructuring" of the technical advisory committee system, with all committees having their independent staff located in the Office of the Commissioner. The Office of the Commissioner was to manage appointments to the committees directly, and committees were to report directly to that office. The Lasagna Committee further recommended that committees be responsible for their own agendas and "more closely monitor" the new drug approval system.

The Lasagna Committee report noted a potential for increased use of advisory committees in the early stages of drug development; in evaluating INDs and NDAs, in setting priorities among drugs; in mediating between the FDA and industry; and in overseeing FDA implementation of committee recommendations. Finally, "to foster close relationships between the government agencies involved with AIDS and cancer drugs, the National

Cancer Institute, the National Institute of Allergy and Infectious Diseases, and FDA should each have a permanent representative sitting as a voting member of the appropriate advisory committee in the other agencies" (p. v).

Other Reports

Two other recent reviews of FDA's performance deserve brief mention, although neither dwelled at length on advisory committees. The Department of Health and Human Services (DHHS) Advisory Committee on the Food and Drug Administration, otherwise known as the Edwards Committee, issued its report in 1991 after a year of considering the FDA's mission, structure, and responsibilities.[7] Its main recommendations addressed these needs: to clarify the FDA's mission and priorities; to elevate the agency's status and authority; to strengthen its enforcement operations; to improve agency management; and to increase its resources.

As part of the recommendation for increased resources, the Edwards Committee stated that "The Commissioner must be empowered, to the limits of statutory authority, to manage the FDA's scientific and technical personnel, and to improve the FDA's access to scientific expertise including advisory committee appointments" (p. v). It noted that the process for recruiting and using advisory committee members was burdensome and costly in time and effort. It cited potential conflicts of interest as a specific reason for the delays and difficulties in appointing and convening advisory committees and as a barrier to the use of "many highly qualified and respected advisors." It advocated prior disclosure of potential conflicts as preferable to premature disqualification when a conflict is anticipated and urged the agency to draw on the Augustine Commission report on the National Aeronautics and Space Administration of March 1991 and the FDA Revitalization Act to reduce the impediments introduced by the current process for managing conflict of interest (pp. 45–46).

The subcommittee on human drugs and biologics of the Edwards committee noted that the FDA appeared to use advisory committees inconsistently and that service on advisory committees had to be made appealing enough to attract the appropriate experts. It recommended both expanded and earlier use of the committees to reduce delays in the approval process. Unlike the Lasagna committee, however, the Edwards committee report opposed the creation of a policy oversight board, but did recommend that the Commissioner increase the accountability and usefulness of the reporting relationship between advisory committees and the FDA. The subcommittee on devices, radiological health, and biomedical research made similar recommendations on advisory committees.

The second report to emerge in 1991 was from the Council on Competitiveness, which responded to many of the Lasagna Committee recommendations.[8] It proposed major changes in the drug approval process—such as contracting with experts outside of the federal government for reviewing drug approval applications. The overall goal of the Council report was to shorten the review and approval process. One recommendation to this end was the increased use of advisory committees for evaluating NDAs and INDs, which, citing Lasagna, meant the use of advisory committees earlier in the research and development process.

THE GOLDFISH BOWL

The reports discussed above indicate, as Hutt has aptly observed, that FDA operates in an environment of intense public scrutiny. Its actions are closely followed by the general public, Congress, the press, the regulated industries, and the financial community. It, as much as any federal government agency, functions in a goldfish bowl. In this section, we consider several aspects of that goldfish bowl—congressional oversight, media coverage, and attention by the financial community.

Congressional Oversight

The FDA interacts with the Congress in many ways. It deals with two legislative committees: the House Committee on Energy and Commerce, and its Subcommittee on Health and the Environment, and the Senate Committee on Labor, Health, and Human Resources, and its Subcommittee on Health. It deals with two other committees for its annual appropriations: the House Committee on Appropriations, Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, and the Senate Committee on Appropriations, Subcommittee on Agriculture and Related Agencies.*

In addition, the House Committee on Agriculture, Subcommittee on Domestic Marketing, Consumer Relations, and Nutrition; the House Committee on Government Operations, Subcommittee on Human Resources and Intergovernmental Relations; the House Committee on Science and Technology, Subcommittee on Oversight; the Senate Committee on Governmental Affairs; the Senate Committee on Agriculture, Nutrition and

* The FDA began as the Bureau of Chemistry of the U.S. Department of Agriculture. Its appropriations continue to be the jurisdiction of the agriculture subcommittees in both Houses of Congress.

Forestry, Subcommittee on Nutrition and Investigations; the Senate Judiciary Committee, Subcommittee on Antitrust, Monopolies, and Business Rights; and the Senate Special Committee on Aging all deal with aspects of the FDA and its programs on a rather routine basis. In short, nearly a dozen congressional committees take an active interest in the affairs of the FDA.

Controversial decisions by the agency or claims of procedural irregularities can quickly result in a hearing before one of these committees, at which the responsible agency officials are called to account. Such hearings usually receive wide media coverage, both from newspapers and television. Frequently, Members of Congress and their staff pinpoint lower echelon FDA officials who are responsible for a given action and invite them into the spotlight of the hearing room. Not surprisingly, this oversight encourages risk-averse behavior on the part of FDA officials well down on the bureaucratic ladder.

Congressional interest in the FDA spans the entire range of the agency's activities. Examples include the following congressional hearings held during the 101st and 102nd Congresses (from 1989 to the present): the generic drug scandal involved 10 hearings on 19 separate days; the amendments to the Orphan Drug Act were the subject of 2 separate hearings; artificial heart valves were considered in 2 separate hearings; and the use of plentopheresis in the treatment of scleroderma was the subject of one hearing. In addition, hearings addressed the reports of the Advisory Committee on the Food and Drug Administration (the Edwards Committee) and the report of the President's Council on Competitiveness on improving the drug approval process.

Media Coverage

Coverage of the FDA by both newspapers and television is copious and growing. The IOM committee sampled one year's worth of articles (June 1991 to June 1992) from *The New York Times, The Wall Street Journal, The Washington Post*, and *The Los Angeles Times* on selected topics before the FDA. Consider the following examples:

- Even though the IOM search of these newspapers began after the FDA had publicly concluded that there was no solid evidence that Prozac, a popular antipsychotic drug, caused suicidal ideation, the four newspapers subsequently carried 11 articles on the drug (4 each in *The Wall Street Journal* and *The New York Times*, 2 in *The Los Angeles Times*, and 1 in *The Washington Post*).
- Similarly, when the FDA reviewed the data on the safety of Halcion, a popular sleeping pill, after its removal from several European markets

because of concerns over its side effects, 18 articles appeared in the four papers (2 in *The Wall Street Journal*, and no fewer than 7 in *The New York Times*).

- Silicone gel breast implants received tremendous attention as the FDA reviewed them for safety and effectiveness in late 1991 and early 1992. The four papers published 167 articles on this topic alone, including 14 editorials. *The New York Times* led with 50 articles and 3 editorials; *The Washington Post* carried 27 articles and 3 editorials.

A glimpse of this intense press and television coverage of the FDA's advisory committee meetings is provided by the item in Box 4-1, which appeared in *The Washington Post* on October 1, 1991.

The Financial Community

The financial community monitors the FDA closely, but the intensity of this scrutiny is a relatively new phenomenon. Indicative of investment community interest in FDA advisory committees was the stock market's response to the advisory committee that dealt with products made by Xoma and Centocor in September 1991, and which recommended approval of the latter firm's antiseptic biologic, and the later response to the FDA's decision in May 1992 to fail to act on this recommendation.

Heightened interest in the financial community recently prompted the FDA to commission a study by Kutak Rock & Campbell, a Washington, D.C., law firm, examining the treatment of financially sensitive information by the agency. The concern of the FDA, as expressed by the November 1991 Kutak Rock & Campbell report,[9] was with "the adequacy of the agency's institutional safeguards against the improper disclosure or use of information about Agency actions [that might] affect the financial markets."

The Kutak Rock & Campbell report examined the FDA's handling of financially sensitive information and proposed general improvements in FDA procedures. Among its general observations, the report noted that procedural inconsistencies increased the risks of inappropriate or unauthorized actions, and specifically, the disclosure of financially sensitive information. The report concluded that "FDA's ultimate goal of adequately and reasonably protecting confidential information can be met in only two ways: by imposing appropriate safeguards or by eliminating the need for confidentially through disclosure." It recommended some new and some modified procedural safeguards and "broader and earlier disclosure" of certain categories of information, with the specific goal of reducing the effects of such disclosures on financial markets.

BOX 4-1 AT AN FDA PANEL HEARING—LIGHTS, CAMERAS, ACTION!

When a panel of experts met recently to consider the evidence for two new drugs against sepsis, a standing-room only crowd of drug company officials, analysts, scientists and reporters packed into a conference room at the Food and Drug Administration headquarters in Rockville to observe.

At stake: an estimated $1 billion market for two new genetically engineered drugs. One analyst told *The Wall Street Journal* the meeting was like "the gunfight at the Rockville corral."

The two drug companies involved—Centocor Corp. of Malvern, Pennsylvania, and XOMA of Berkeley, California—brought their own TV crews to record the event.

CNN was there. So was a row of trade journal reporters and other news media. Iley scribbled notes with one hand and held tape recorders in the other. Two photographers set up tripods in a corner and methodically clicked three shots of every data-filled slide with telephoto lenses.

Men dressed in striped shirts and bow ties, their cuffs adorned with gold, reached for compact cellular phones throughout the day. They whispered the latest word decided by an 11-member advisory panel to the FDA and a panel of experts who advised the advisory panel.

Drug company representatives made well-rehearsed presentations about the results of their clinical trials. Experts questioned their work.

By the day's end, the FDA panel had decided that Centocor's HA-1A was safe and effective but stopped short of recommending that it be licensed. A decision on E5, the XOMA drug, was postponed for more reviews as three rows of company officials glumly looked on.

But the shootout wasn't necessarily over, since as FDA spokeswoman Faye Peterson later noted, all panel decisions are recommendations only. It's up to another FDA body to decide when and if each drug goes to market.

Sally Squires
Washington Post "Health" section, p. 12
October 1, 1991

As mentioned above, the report devoted a chapter to FDA advisory committees and the attention they receive from the financial community. Historically, it noted, the FDA's final decisions on approving or disapproving a drug usually agree with the prior recommendations of advisory committees. As a result, the financial community pays great attention to the discussion and final recommendations at an advisory committee meeting.

This attention is broader than a simple concern for the product being reviewed:

> The meetings also provide some insight into the views of FDA about the product, and thus serve as predictors of the likelihood and speed of product approval by the Agency. Indeed the [financial] analysts regard the mere scheduling of an advisory committee meeting for a product as an indication that FDA will reach a decision about a product within a relatively short time.[10]

Given the intense interest of the financial community and the effect the advance public release of questions prepared for the advisory committee might have on trading in the securities markets, the report basically concurred with current FDA practice of publicly releasing such questions on the morning of a committee meeting. Advisory committee members, as special government employees, the report noted, are subject to federal conflict of interest statutes. Consequently, "the regulatory prohibitions against disclosure of 'inside information' by SGEs are more stringent, more explicit, and far lengthier than the ones for actual FDA employees." But advisory committee members receive no particular training about safeguarding financially-sensitive information, and might themselves be sources of information leaks about a product's position in the approval process according to several of the FDA employees interviewed by Kutak Rock & Campbell. Among its many recommendations, therefore, the report proposed that training materials for SGEs be expanded to explain the importance of these issues.

CONCLUSIONS

In general, from the history of the FDA advisory committee system (chapter 2), the analysis of the current system (chapter 3), and the examination of the foregoing reports and the environment of public scrutiny in which the agency operates, the following preliminary conclusions emerge.

1. It is worth asking why the recommendations of these prior reports have not resulted in a well-organized, efficiently functioning FDA advisory committee system. The answers are far from clear but several hypotheses may be advanced. One possibility is that financial resources have always been too scarce for the agency to give sufficient attention to the system. A second hypothesis is that recommendations about advisory committees have tended to be buried in higher priority concerns about the drug approval process. Yet a third explanation is resistance by the FDA professional staff. Equally

plausible is the argument that the top leadership of the agency has not devoted adequate sustained attention to advisory committees, including efforts to institutionalize them with clear authority, strong management, and sufficient resources. Finally, it may be that FDA advisory committees lack a political constituency comparable to the support of academic medicine for the NIH study section system.

These hypotheses cannot be tested in any scientific way and remain the bases for speculation and argument. Notwithstanding the range of possible answers to the question about the limited impact of prior reports, we optimistically hope that the reception accorded to this report will be different.

2. A wide consensus exists that the primary purpose of the FDA's technical advisory committees is to bring independent scientific expertise to bear on agency decisions. The agency affirms this view, industry endorses it, and the medical community clearly believes in this premise.
3. The various interested parties begin to diverge, however, in their views of their benefits of technical advisory committees. The agency sees their benefits as providing technical assistance on questions before it, adding credibility to the decisions it makes and to its decision-making procedures, and providing a public forum in which it can ventilate controversial issues and hear from directly affected interests. For the public, and especially Congress, advisory committees have helped legitimize the scientific bases for FDA decisions and have come to be seen as a counterweight to both bureaucratic overreaching and caution. Industry has become more supportive of these committees over time because it believes they have been more strongly oriented toward therapeutic innovation than the agency and that they provide some opportunity for fair review of agency decisions that would otherwise go unscrutinized.
4. The FDA experience with advisory committees, both historically and currently, reveals that their use has usually resulted from agency initiative. Consequently, agency officials have generally determined the functional roles that advisory committees will play, what matters they will consider, when they will be asked to provide advice, what information they will be given, and—very clearly—what weight their advice will have.
5. Technical advisory committees are seen both within FDA and by most external observers as *advisers* to the agency. They are not judicial bodies, save in their infrequent use as appeals bodies. Thus, their charge is not to adjudicate competing claims but to provide independent advice to the agency on the questions on which the agency decides it needs advice.
6. A major rationale for use by the FDA of outside expert panels in the 1960s and '70s—especially in the National Academy of Sciences-National Research Council Drug Efficacy Study, the Over-the-Counter drug review

panels, and the biologics review advisory committees—was to clear a backlog of work that the agency was not equipped to handle because it had too few professional staff and these were often lacking in the needed technical competence. This workload-clearing function of advisory committees is seldom advocated today.

7. The proposition that advisory committees would speed the product approval process, especially for drugs, has been advanced on a number of occasions, usually without strong supporting analysis. "The IOM committee believes that the justification of advisory committees derives less from their effect on the efficiency of the product evaluation process and more from their impact on the quality of that process. In that regard, advisory committees reflect the agency's desire for expert advice, for credible decisions and decision-making processes, and for the ability to discuss controversial issues in a public arena.
8. An underlying issue is the independence of advisory committees from sources that might wish to influence the outcomes of their deliberations. These sources include product sponsors and, in particular, agency officials. Consequently, this report takes up the matter of independence in the narrative and recommendations of the next four chapters.
9. A continuing fact of life for the FDA is the environment of intense public scrutiny within which it operates. Consequently, any significant changes in how the agency functions require some working consensus that includes the agency, its leadership, and its large cadre of professionals; the Congress; the Executive Branch, from the White House to the Secretary of Health and Human Services and the other agencies of the Public Health Services; the regulated industries—pharmaceuticals, biotechnology, and medical devices; the academic medical science community; and organized groups representing the consumers, voluntary health organizations, and the public.

The following four chapters examine analytically many of the issues that have concerned the designers, managers, and users of the advisory committee system over time. Chapter 5 deals with committee membership issues. Chapter 6 examines conflict-of-interest issues in great detail, as well as the matter of scientific bias. A cluster of issues concerned with committee operations is addressed in chapter 7. Finally, in Chapter 8, the organization and management of the advisory committee system is considered.

NOTES

1. Peter Barton Hutt, "Investigations and Reports on the *Food and Drug Administration*," in *Food and Drug Law, Food and Drug Law Institute* (Washington, D.C., 1991), p. 48.

2. U.S. House, Committee on Government Operations, *Use of Advisory Committees by the Food and Drug Administration*, 11th report, based on a study by the Intergovernmental Relations and Human Resources Subcommittee, 94th Cong., 2nd Sess., Report No. 94-787 (January 26, 1976).

3. Stockman, Paul K, Applicability of the Federal Advisory Committee Act to Alternative Sources of Scientific Input, report to the IOM FDA advisory committee study (July 31, 1992).

4. Department of Health, Education, and Welfare. *Review Panel on New Drug Regulation: Final Report* (Washington, D.C., May 1977).

5. Commission on the Federal Drug Approval Process, *Final Report* (Washington, D.C., March 31, 1982).

6. President's Cancer Panel, National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS. (Washington, D.C., August 15, 1990).

7. U.S. Department of Health and Human Services. *Final Report of the Advisory Committee on the Food and Drug Administration* (Washington, D.C., May 1991).

8. Council on Competitiveness. *Fact Sheet: Improving the Nation's Drug Approval Process* (Washington, D.C., 1991).

9. Kutak Rock & Campbell. *FDA Safeguards Against Improper Disclosure of Financially-Sensitive Information* (Washington, D.C., November 1991).

10. Ibid., p. 69.

5

Committee Membership

FDA regulations differentiate between policy advisory committees and technical advisory committees. This report deals mainly with technical committees. The regulations also distinguish between voting and nonvoting (or representative) members. This chapter deals primarily with voting members of technical advisory committees, although representative members are also discussed.

The ability of the Food and Drug Administration to attract and retain qualified individuals as members of its technical advisory committees is critical to the successful performance of the advisory committee system. A general criterion for voting members is that they must have "expertise in the subject matter with which the committee is concerned" (21 CFR 14.80(b)(1)-(i)).

The "subject matter" of advisory committees, as indicated elsewhere in this report, pertains to the evaluation of drugs, biologics, and medical devices regarding their safety and effectiveness, including indications and contraindications for use and related issues of labeling, and to broader technical issues of product evaluation, such as specific methodologies for assessing a particular class of therapeutic agents.

In this chapter, we address the criteria for membership, recruitment procedures, appointment authority, and provision for consumer and industry representatives on advisory committees.

NOMINATION CRITERIA

General and Specific Criteria

The range of products that the FDA regulates is extensive, and the expertise it needs is equally great. Consequently, the FDA initiated its advisory committee system as a way to obtain scientific and clinical advice that was not available to it through its professional staff but that was needed

to carry out its regulatory responsibilities regarding drugs, biologics, and medical devices.

The scope of a single advisory committee may also be quite broad; some topics may constitute a discipline or subspecialty in themselves. Consequently, the agency needs a broad array of expertise, both clinical and nonclinical; it also has an interest in selecting and recruiting advisory committee members who are recognized by their peers for their professional competence. The FDA regulations cited above do not go beyond the general criterion of "expertise in the subject matter" to address specific qualifications or desired characteristics for advisory committee membership. Here, we examine the qualifications.

It is only reasonable that if candidates are being sought for technical advisory committees, scientific or technical competence should be the primary criterion. The IOM committee believes that the advisory committee system will function most effectively and best serve the needs of the public and the agency if the FDA routinely attracts and retains individuals who meet a high standard of excellence as clinicians and scientists.

The IOM committee strongly endorses the criterion or scientific or technical competence as a requirement for selecting all voting members of FDA technical advisory committees.

The IOM committee adopted the view that the competence needed on an advisory committee should include the clinical expertise necessary to evaluate a sponsor's submission.[*] This expertise involves not only clinicians and scientists from the pertinent disciplines but clinical investigators who are experienced in the design, conduct, and interpretation of drug or medical device clinical trials. However, in its deliberations the IOM committee did not support the view that the FDA should develop guidelines to define either the minimum or the optimum level of qualifications or expertise for potential advisory committee members. The reasons for not pursuing this course are indicated later in the discussion of "balance."

Diversity Objectives

In this context, the IOM committee acknowledges that "diversity goals" of gender, race-ethnicity, and geography guide the selection of advisory committee members. In the committee's view, these diversity goals are not incompatible with the criterion of scientific and technical competence but

[*] The Industry Liaison Panel, which advised the committee, strongly emphasized this viewpoint.

reflect legitimate policy objectives of a pluralistic society that are well founded, appropriate, and designed to ensure a range of viewpoints on what are seldom purely technical issues. The committee believes that it is impractical and undesirable to consider retreating from these general goals.

In composing an advisory committee, the FDA has traditionally followed Department of Health and Human Services (DHHS) policies, which aim at a target committee roster composed of 20 percent women and 10 percent minorities. The IOM committee recognizes that the agency, some advisory committee members, and some external observers regard these goals as onerous and tending, on occasion, to undermine the quest for scientific and clinical excellence. There are reports that staff of the three centers* spend considerable time and effort in identifying and recruiting individuals who represent these demographic characteristics and that some individuals with greater expertise may be excluded as a result.

This particular recruitment problem has several sources. Historically, it stems from the relatively few women and minority members of medical and scientific professions, especially in highly specialized fields. Other factors include the difficulties of identifying such individuals and a low rate of acceptance of appointment to FDA advisory committees by identified individuals from these groups.**

The identification problem stems in part from the fact that the agency's current practices are insufficient to uncover a critical mass of these candidates. Women and minorities may be underrepresented in the leadership of professional societies, where peer contact is established and maintained, and in the professional literature, both of which are used extensively by the FDA in seeking candidates for advisory committee vacancies.

The IOM committee believes that meeting FDA's diversity goals may require special efforts by the agency to identify women and minority group members who are scientific and medical experts.

The IOM committee recommends that the FDA continue its policy of actively seeking qualified women and members of minority groups as potential candidates for advisory committee membership.

* These are the centers for Drug Evaluation and Research (CDER), for Biologics Evaluation and Research (CBER), and for Devices and Radiological Health (CDRH).

** The low acceptance rate problem seems to be a particularly pernicious issue and one that is not peculiar to women and minority candidates.

The FDA should waive this policy, however, in those infrequent cases in which the number of women and minority candidates in a field is so limited that it is not feasible to expect to be able to recruit them to serve on a committee.

Some constraints may limit the access of the Food and Drug Administration to scientific and technical competence as it seeks to meet its diversity objectives. Current policy of the DHHS prevents an individual from serving concurrently on more than one Public Health Service advisory committee without a special departmental waiver. This policy limits the expertise that can be tapped for a particular committee and impedes meeting diversity objectives. Thus, for example, some highly qualified individuals who may be serving on National Institutes of Health (NIH) study sections are precluded from service on an FDA advisory committee, and vice versa.

The IOM committee recommends that the Department of Health and Human Services eliminate its policy prohibiting dual committee membership and that qualified candidates for FDA advisory committees be allowed to decide whether they wish to serve on more than one Public Health Service committee. However, it recommends that the Food and Drug Administration exhaust other means of recruitment before it resorts to selecting persons who serve on other advisory committees.

Balance

The Federal Advisory Committee Act (FACA) requires that advisory committee membership be "fairly balanced in ... the points of view represented and the functions to be performed" and that there be "appropriate provisions to assure that the advice and recommendations of the advisory committee will not be inappropriately influenced by ... any special interest, but will instead be the result of the advisory committee's independent judgment" [FACA §5(b)]. This criterion, however, provides little operational guidance to the nomination and selection of members to serve on committees like those at FDA.

This "balance" requirement, as a practical matter, cannot be easily applied to FDA technical advisory committees, because it contemplates balancing known or assumed divergent views. Achieving fair balance, for example, on a labor-management relations advisory committee, would lead to the appointment of representatives of both industry and organized labor. For technical advisory committees responsible for advice on a wide and unpredictable range of issues, the solution is less obvious.

In the case of technical advisory committees, "balance" should be interpreted as a mix of relevant scientific disciplines and a diversity of

scientific views. The critical skills may sometimes be broad, at other times narrow and deep; they may be the added experience and wisdom of senior figures in a field, in addition to technical expertise, or the energy and willingness to examine technical data in great detail characteristic of junior "workhorses." At times, they may require experience in the design and conduct of clinical trials, or the analysis and interpretation of data, as well as knowledge of patient care. At other times, elusive "committee skills" may be needed to ensure the effective performance of an advisory committee.

The balance of viewpoints required on a given advisory committee cannot be specified easily in advance of a specific meeting agenda. Consequently, a general commitment to expertise and excellence, limited only by legitimate "diversity goals," is appropriate as a statement of agency policy. The IOM committee believes, and court decisions now support, that it is ultimately the Commissioner's responsibility to see that such balance is achieved.

The IOM committee considered the wisdom of recommending that "balance" be interpreted as committee membership that included representatives (or advocates) of specific constituencies, irrespective of scientific competence. The committee rejected this concept on the grounds that the primary role of advisory committees is to provide the agency with the best scientific interpretations and advice and not to represent specific constituencies. Furthermore, under "Committee Operations" the IOM committee recognized the importance of input to advisory committee deliberations from nonscientific sources such as patients, industry, and consumer groups and concluded that such input can be best achieved by public testimony that relates directly to the specific agenda of an advisory committee meeting.

Implications

Three implications flow from the above discussion. First, the FDA should formally organize the recruitment of advisory committee members in a systematic, aggressive way (not simply in a passively formal and variably active informal way as at present). Second, recruitment should be oriented toward increasing the pool of potential advisory committee members from which candidates are selected, rather than simply filling vacancies. Third, in the absence of detailed specific selection criteria, and the ability of this or any other committee to design such criteria, it is imperative that advisory committee member recruitment be given the sustained, continuing attention of agency professionals from the Office of the Commissioner down through the centers, offices, and divisions responsible for product evaluation. Executive secretaries should be deeply involved in recruitment, as many of

them are now, but the recruitment function should not be delegated exclusively to them.

The issue of balance arose in the IOM committee's Industry Liaison Panel recommendation that the composition of a given advisory committee be tailored to the expertise required by a specific meeting's agenda. These "custom tailoring" possibilities are now open to the agency as a result of the rechartering of advisory committees in all three centers. The advantages and disadvantages of this approach are discussed in detail in Chapters 7 and 8; they are not considered here because they do not affect the recommendations on member recruitment.

RECRUITMENT PROCEDURES

The FDA currently recruits advisory committee members through a mix of formal and informal means. FACA defines the formal procedure, which involves an annual *Federal Register* notice (21 CFR 14.80(b)(1)(i)). The annual notice lists the specific advisory committees for which it is known that vacancies of voting members will occur in the next 12 months; also published is a list of committees for which vacancies are not expected but may occur. The *Federal Register* notice requests nominations for voting members to fill these vacancies and for candidates for potential vacancies.

Any interested person or group, including industry, may nominate one or more individuals. The regulations require that a nomination specify the advisory committee for which the nominee is recommended, include a complete curriculum vitae of the nominee, and state that the nominee is aware of the nomination, is willing to serve, and appears to have no conflict of interest that would preclude membership. Although few advisory committee nominees and fewer members result from the *Federal Register* process, it is the only existing agency-wide formal mechanism for identifying and recruiting a pool of potential nominees.

Most nominations result from informal processes. Interviews with the CDER, CBER, and CDRH division and office directors and executive secretaries identified the following sources of nominees:

- Recommendations by professional societies.
- Contacts made by FDA staff at professional society meetings.
- Referrals by former or outgoing FDA advisory committee members (not limited to a particular committee, FDA division, or center).
- Personal inquiries by an FDA professional based on his or her knowledge of experts in a particular field.
- Identification of experts in the medical literature.

Many variations exist in the informal recruitment processes discussed above as a result of the different approaches of particular FDA recruiting officials and the absence of any clear agency-wide policy beyond the *Federal Register* notice.

The IOM committee recommends that the FDA adopt an agency-wide recruitment policy and develop a more systematic approach to seeking nominations on a continuing basis for potential advisory committee membership. The agency should actively seek nominees from many sources—academic medicine, professional societies, other government agencies, industry, and consumer and patient organizations. It should not rely solely on its own staff for such nominations. Each center should develop and periodically update a pool of qualified candidates, rather than simply seek nominations to fill vacancies.

The FDA should use multiple approaches to develop these candidate pools, including use of the NIH-Alcohol, Drug Abuse, and Mental Health Administration computerized file (as well as maintenance and updating of this data base); creation of an FDA computerized data base; routine nominee solicitation of current and former advisory committee members, professional medical and scientific societies, medical school deans and department chairmen, industry, and interested consumer and public interest organizations. The FDA should explore avenues for seeking nominations such as announcements in the *Journal of the American Medical Association*, the *New England Journal of Medicine*, and specialty journals. Routine solicitation could be extended to identify candidates for consultancies as well as advisory committee members.

In addition to aggressively seeking nominations from medical and scientific societies, the FDA should seek to enlist these organizations in the routine support of the advisory committee nomination process.

The IOM committee, addressing itself to these medical and scientific societies, urges them to accept as a continuing obligation the identification and nomination of individuals to the pool of potential FDA advisory committee members.

External endorsement, however, should constitute only input to the FDA; it should not involve the review of nominees or selection of candidates.

The NIH Office of Research on Women's Health and similar organizations should be routinely solicited for nominations. Professional society groups, such as the Women in Nephrology of the American Society of

Nephrology, should also be enlisted in this effort. Working groups of women and minority medical science experts should be routinely asked to identify candidates for the pool.

The IOM committee disagreed with the recommendation of the Industry Liaison Panel that "an impartial group, such as the Institute of Medicine, [should] review proposed additions to the drugs and biologics advisory committee roster to ascertain that all individuals are, indeed, recognized as experts by their peers." (The Lasagna Committee advanced a similar recommendation.) Rather, the IOM committee believes that the recruitment of potential candidates and the nomination and the appointment of members are functions that should be exercised by the FDA and that the agency should be held accountable for their effective performance. It understands its needs for advice better than any external organization.

The responsibility for implementing these steps within the FDA should not be delegated by neglect solely to executive secretaries. Although these individuals may well do the lion's share of the work in recruiting advisory committee members, the Commissioner of Food and Drugs should issue clear guidance to all FDA staff that the responsibility must be discharged at the center, office, and division levels as well.

CONSUMER MEMBERS

The FDA seeks two types of consumer participation in its technical advisory committees—nonvoting consumer representatives for its CDRH advisory panels and consumer-nominated, technically qualified members for its CDER and CBER committees.

FDA regulations list as a standard that an advisory committee must meet "whenever feasible, or required by statute, [a committee] include representatives of the public interest" (21 CFR 14.40(f)(5)). Although the regulations are silent on the meaning of "representatives of the public interest," they later state (21 CFR 14.80(b)(2)) that the Commissioner

> shall, when required by statute, and may when not required by statute, provide for *nonvoting members* of a technical advisory committee to serve as *representatives of and liaison with interested organizations* [emphasis added]. Nonvoting members—(i) Shall be selected by the interested organizations, as provided in 14.84; technical expertise in the subject matter with which the committee is involved is not a requirement; and (ii) May be special Government employees subject to the conflict of interest laws and regulations, except as provided in 14.84(e).

The procedures for nomination and selection of nonvoting members of standing technical advisory committees are specified in 21 CFR 14.84. The "rights and responsibilities" of these members are delineated in 21 CFR 14.86.

There are no nonvoting consumer or industry representatives who serve on drug or biologics advisory committees. In the 1970s, nonvoting consumer representatives served on drug advisory committees, but there were no industry representatives. These nonexperts were often unable to participate in committee deliberations. Consequently, the then-Bureau of Drugs decided on a different approach. It now seeks consumer-nominated individuals who are technically qualified to serve as voting members of drug and biologics advisory committees. All drug and two of four biologics advisory committees now have such members.

The Medical Device Amendments of 1976 required that all advisory committees or panels include one nonvoting consumer representative and one nonvoting industry representative. In accordance with 21 CFR 14.80(b)(2), these individuals are to represent interested organizations and provide liaison to the advisory committee. These nonvoting members are not required to be expert. The IOM committee considered and rejected the extension of the statutorily required CDRH approach of nonvoting consumer and industry representatives, but it also chose not to recommend modification of the device provision of the law.

Currently, the FDA Office of Consumer Affairs (OCA), which is responsible for seeking consumers to serve as advisory committee members, solicits nominations from a number of sources. It does so both for the CDRH nonvoting consumer representatives and for the CDER and CBER consumer-nominated, technically qualified voting members. The OCA is assisted in this process by a consortium of consumer organizations that identifies and evaluates individuals who are technically qualified to serve on FDA technical advisory committees and who also have ties to consumer organizations. Along with other interested parties, the consortium nominates individuals for appointment both as qualified voting members of CDER and CBER committees and as consumer representatives of CDRH panels. The consortium's principal role is to interview consumer nominees on behalf of FDA and evaluate their qualifications.

In seeking nominees from consumer organizations, the FDA should continue to solicit nominations from the consumer consortium, but it should also reach out to other interested parties. In the judgment of the IOM committee, the practice of allowing any outside organization to screen (and thus to screen out) nominees from other sources is unsound.

In addition, the IOM committee believes that the concept of "consumer"—both for consumer-nominated members and medical device consumer

representatives—should be expanded to include patients or patient-nominated individuals, whose viewpoints can be valuable in the product evaluation process.

The IOM committee believes that consumer input to the deliberations of FDA technical advisory committees can be quite valuable. It recognizes that there are various ways to obtain such input, especially through public testimony by consumers or patients as appropriate to the specific agenda.

The IOM committee recommends that the FDA actively seek technically qualified nominees from consumer organizations and other interested parties for all of its technical advisory committees and panels. Selection, however, should require evidence of scientific and technical qualifications. The committee also recommends that the concept of "consumer" be expanded to include patient and patient-oriented organizations. Furthermore, no private individual or organization should be given the right to screen nominations from other sources on behalf of the agency.

APPOINTMENT AUTHORITY

Until early 1991, the Secretary of Health and Human Services appointed members of FDA technical advisory committees. This sometimes resulted in nominees who may not have been scientifically qualified or who were selected to bring a politically preferred view on scientific and regulatory matters before the FDA. Following enactment of the Food and Drug Administration Revitalization Act of 1990, the Commissioner has appointed advisory committee members, but he remains under an obligation to send nomination packages to the Office of the Secretary 10 days in advance of any appointment.

The IOM committee believes that vesting power to appoint committee members in the Commissioner constitutes a substantial step forward in both expediting the appointment process and ensuring that such appointments are responsive to the specific scientific and technical needs of the agency.

The IOM committee commends the Office of the Secretary for its concurrence that the Revitalization Act vests formal authority to appoint advisory committee members in the Commissioner of Food and Drugs.

ADMINISTRATIVE RESPONSIBILITY FOR APPOINTMENTS

The Commissioner, under his authority to appoint advisory committee members, should clearly indicate to all FDA staff that center directors, office

and division directors, and executive secretaries share responsibility for recruiting qualified advisory committee members. Nominations to the Commissioner should come from the center directors.

The IOM committee recommends that the job descriptions of the FDA center, office, and division directors, and of the executive secretaries be expanded to reflect their responsibilities for recruiting, nominating, and recommending advisory committee members.

6

Ensuring Committee Integrity

This chapter deals with two important issues: How should the FDA protect the deliberations of its advisory committees against potential financial conflicts of interest on the part of individual committee members? And what steps should the agency take to guard against possible intellectual bias of committee members. The committee dealt with the first of these issues extensively, giving it more attention than any other single subject. It was specifically asked to do so by the FDA Commissioner Kessler, because this perplexing issue was affecting the agency's ability to use advisory committees in the evaluation of new products.

We use "intellectual bias" to refer to a different concern, namely, the possibility that a committee member may be so convinced about the right answer to a question of science or medicine—or so clearly identified with a particular view—that he or she may not be (or appear to be) able to approach a matter before the committee with an open mind. This concern is sometimes discussed under the label "conflict of interest," but the committee has treated it separately precisely because the federal law contains an elaborate set of restrictions addressed solely to the matter of financial conflict.

Concern about intellectual bias, which is addressed in the final section of this chapter, proves to be equally perplexing and may assume comparable importance at the FDA. But it came into clear focus only near the end of our study, and thus has received less thorough discussion and assessment. The topic is a candidate for further attention in connection with the work of the FDA advisory committees, just as it is now receiving extensive scrutiny and debate among policymakers and academic scientists who confront it in other contexts.

Potential financial conflict of interest and intellectual bias are obviously critical matters for the Food and Drug Administration and for the public. For the FDA's advisory committees to serve their purposes, their judgments must be—and must be seen to be—the product of the members' independent

assessment of the scientific evidence presented to them. At the same time, the criteria by which candidates for committee appointment are screened and the participation of appointed members is regulated must be both realistic and fair. These criteria must protect the agency's processes from real risks of inappropriate influence and yet not disqualify or embarrass all scientists and clinicians who have had any connection to the drug, biologics, or device industries.

The chapter deals first with financial conflict of interest, indicating the origins of the IOM committee's concern for this issue, reviewing the statutory framework that governs the area, examining the system by which the FDA administers the conflict-of-interest laws, analyzing the rapid changes in that system, including a number of controversial cases and some encouraging prospects for improvement, and concluding with a number of recommendations. The chapter addresses the issue of intellectual bias in a concluding section.

FINANCIAL CONFLICT OF INTEREST

The reality facing the FDA is that over the past decade, perhaps longer, sponsors of drugs, biologics, and devices have turned increasingly to academic researchers to help develop and test new products. This pattern is particularly obvious in the biotechnology industry. Consequently, many of the same experts whose advice the FDA wishes to obtain have affiliations with regulated firms, some with many such firms. The recognized expertise of such individuals makes them attractive to both government and industry.

In addition, the agency has sought advisory committee advice on a growing range of scientific and regulatory issues, and it is under pressure to increase the agenda items considered by its committees. One result of these coincident developments has been to generate potential financial conflicts of interest for one or more committee members in connection with every committee meeting.

The tensions that result from this set of relationships cannot be eliminated but must not be ignored. The goals of any system for mediating these tensions must be to protect the integrity of the FDA's decisions and at the same time to allow the agency access to essential expertise. The IOM Committee is concerned that the current system for managing potential financial conflicts of interest, as now administered, may be jeopardizing the latter goal without significantly advancing the first.

When Commissioner Kessler met with the IOM Committee on December 6, 1991, he emphasized his desire for guidance in "solving" the FDA's current problems with conflict of interest and its advisory committees.

The Commissioner stressed that, "If [the committee] does nothing else but solve our conflict of interest problem, then we will have been well served."

However, neither the Commissioner then nor the FDA senior staff later provided the Committee with a detailed picture of this "conflict-of-interest problem." The full dimensions of the problem were not then appreciated, we believe, because they were undergoing significant change even as the study began. It took the better part of this study for the Committee and its staff to gain an understanding, which may still be incomplete, of the "problem."

The IOM committee entertained the hypothesis that numerous members of the FDA advisory committees were participating in decisions in which they had significant personal financial interests—with or without permission to do so. We did not find evidence that this was the case.

The IOM committee also considered the possibility that the "problem" was basically one of perception—a widely held belief that some advisory committee members, even if not in violation of the law, were compromised by their relationships with industry. Although it is not easy to measure public perceptions on such a matter, and we have not attempted to do so, the committee believes this is not a trivial concern. The range of relationships that the current law, as interpreted, treats as presumptively disqualifying financial interests has become so broad that virtually no advisory committee member is untouched. Thus the FDA confronts the need to consider granting conflict-of-interest waivers for one or more members at almost every meeting, creating or bolstering an impression that the system is seriously compromised.

In the committee's judgment, however, the core of the problem, or at least the portion on which thoughtful recommendations might make an immediate contribution, is internal to the FDA and the department. The problem resides in the system for identifying potential financial conflicts, for the agency's determining whether to seek a waiver (which is specifically provided for in the governing law) that would permit the participation of a specific member in advisory committee deliberations, and for evaluating that request for a waiver in a particular case.

A sometimes bewildering number of organizational entities are involved in administering conflict-of-interest laws. They are identified in Table 6-1 on the following page.

Table 6-1 The FDA Conflict-of-Interest Players

Food and Drug Administration
CDER, CBER, and CDRH and their respective committee management staffs
Division of Ethics and Program Integrity (DEPI)
Committee Management Office
Office of the Chief Counsel, FDA
Department of Health and Human Services
Office of the Special Counsel for Ethics (OSCE), in the Office of the General Counsel
Other Federal Agencies
Office of Government Ethics (OGE)
General Services Administration (GSA)
Department of Justice
Office of Personnel Management (OPM)
Office of Management and Budget (OMB)

THE STATUTORY FRAMEWORK

A familiarity with the current federal conflict-of-interest law as it applies to the FDA advisory committee members is necessary to understand the "problem" that Dr. Kessler asked us to evaluate. The key statutory provision is 18 U.S.C. §208, which is part of the U.S. Criminal Code, and it applies to all federal government employees. Members of the FDA's technical advisory committees are covered because they are appointed as "special government employees" (SGEs) who serve the government on a part-time or intermittent basis.* Appointment as an SGE allows an advisory committee member to be paid and compensated for expenses; it also facilitates disclosure to committee members of confidential or proprietary information, which is often the bulk of the material in a drug, biologic, or device application.

Section 208 (summarized in Table 6-2) has two main parts. Subsection (a) prohibits (i.e., makes criminal) a government employee from participating "personally and substantially" in any "particular matter" in which, to his/her knowledge, "he, his spouse, minor child, general partner, organization

* As defined in the FDA Staff Manual Guide 3118.6, April 18, 1986, this category includes "anyone who is retained, designated, appointed or employed to perform services with or without compensation for a period not to exceed 130 days during any period of 365 days whether on a fulltime or intermittent basis."

in which he is serving as officer, director, trustee, general partner, or employee, or any person or organization with whom he is negotiating or has any arrangement concerning prospective employment, has a financial interest."* The law does not distinguish among types of financial interests, nor between large and small or significant and insignificant interests. By common consensus it goes well beyond such things as monetary payments or marketable securities.

This broad reach of subsection (a) is qualified by subsection (b), which allows for three exceptions (or waivers) to this general prohibition. Subsection (b)(1) allows the official responsible for appointing an employee to grant an exception to participate in a matter in which the employee's interest "is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect." Subsection (b)(2) authorizes the promulgation of regulations that categorically except certain types of interests. As the law was amended in 1989, this authority can be exercised only by the Office of Government Ethics (OGE). Finally, subsection (b)(3), which was added to the law the same year, exclusively for advisory committee members, allows the official responsible for appointing a committee member to grant an exception if he/she concludes that the agency's need for the member's service in the particular matter outweighs any risk that this impartiality will be compromised. Each of these three waiver authorities is examined in greater detail below.

* Section 208(a) reads: "Except as permitted by subsection (b) hereof, whoever, being an officer or employee of the executive branch of the United States Government, ... including a special Government employee, participates personally and substantially ... through decision, approval, disapproval, recommendation, the rendering of advice, investigation, or otherwise, in a judicial or other proceeding, application, request for a ruling or other determination, contract, claim, controversy, charge, accusation, arrest, or other particular matter in which, to his knowledge, he, his spouse, minor child, general partner, organization in which he is serving as officer, director, trustee, general partner or employee, or any person or organization with whom he is negotiating or has any arrangement concerning prospective employment, has a financial interest—shall be subject to the penalties set forth in section 216 of this title."

Table 6-2 Federal Conflict of Interest Law Affecting Advisory Committee Members (18 USC § 208)

Section of Statute	Bases for Determination of Financial Conflict	
208(a), **from 1978 Ethics in Government Act**	Prohibits any federal officer or employee from participating personally and substantially in a particular matter in which, to his/her knowledge the employee, his/her spouse, minor child, or general partner, an organization in which he/she is serving as an officer, director, trustee, general partner, or employee, or a person or organization with which he/she is negotiating for or has an arrangement concerning prospective employment has a financial interest.	
Types of Waivers	Test for Granting Waiver	Current Status
208(b)(1), **from 1978 Ethics in Government Act**	If the FDA Commissioner determines that "the employee's interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect."	Now used by FDA for consultants; formerly used for advisory committee members
208(b)(2), **amended by 1989 Ethics Reform Act**	If the FDA Commissioner, on the basis of the OGE government-wide rule, determines that an employee's interest "is too remote or too inconsequential to affect the integrity of the services."	OGE rule not yet proposed; agencies with such a rule the 1989 Ethics Reform Act may continue to use it until the OGE issues its rule; the FDA lacks such a rule
208(b)(3) **added in 1989 Ethics Reform**	If the FDA Commissioner determines for an advisory committee member that "the need for individual services outweighs the potential for a conflict of interest created by the financial interest involved."	Now used by the FDA for all committee members; requires that the OSCE and the OGE occur.

Subsection 208(b)(1)

Subsection (b)(1) permits the government official responsible for appointing the employee to issue an advance written determination, a (b)(1) waiver, finding that "the employee's interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect." Although this language appears to require an assessment of the magnitude or character of the employee's interest, the section allows consideration of other factors, according to the OGF. These include the magnitude of the employee's other holdings (e.g., as a way of asking "how much would it really matter if his/her stock in Company X doubled in value?"), the likelihood that the interest could be materially affected by a decision made or advised on by the employee, and the type of interest involved). The presence of subsection (b)(1) in the law arguably supports the conclusion that section 208(a) covers *any* financial interest, no matter how small.

Under a 1990 Executive Order, an agency that contemplates granting a (b)(1) exception must first "consult" with the OGE if it is practical to do so. This does not necessarily mean that the OGE must approve the agency's decision. Any (b)(1) exception granted without consultation with, or even in defiance of advice from, the OGE will nonetheless be valid. However, under DHHS policy, any exception granted under (b)(1) does require approval by the Office of the HHS Special Counsel for Ethics. In other words, the Commissioner is not authorized to approve a waiver without OSCE approval.

Subsection 208(b)(2)

Subsection (b)(2) of section 208 authorizes the issuance of regulations that categorically exempt certain classes of financial interests as being "too remote or too inconsequential to affect the integrity of the service of the" employee. Before the 1989 amendment of (b)(2), individual agencies had authority to grant such categorical waivers; if they did so, those regulations remain in effect today. After the legislation, however, the power to issue such regulations was lodged exclusively in the OGE, and agencies without these rules are now precluded from issuing them. Since the FDA had no (b)(2) regulations before the 1989 amendments, and because the OGE has not yet issued such regulations, the FDA has no basis to grant (b)(2) waivers.

The language of subsection (b)(2) allows class exemptions based on either of two criteria. The interest may be "too inconsequential," i.e., too small, which implies an absolute criterion independent of the likelihood that

an interest might be affected or, even if affected, might threaten an employee's integrity. Alternatively, the interest may be "too remote," which seems to speak to the likelihood that the value of the interest would not be affected by the advice given or by any decision based on that advice. Pursuing the latter prong, subsection (b)(2) might allow the OGE to issue a regulation exempting endowment holdings of educational institutions from the class of employer financial interests that would otherwise disqualify an advisory committee member.

The OGE says it is developing regulations to implement (b)(2). As described to the IOM committee, the regulations will speak to both the magnitude and type of interests and to the functions performed. They may initially cover only ownership interests in business enterprises, e.g., shares of stock and perhaps other equity interest such as partnerships.

Thus far the OGE has not developed, and may not even have considered, criteria for evaluating the remoteness of other types of interests, such as research grants. However, the DHHS Special Counsel for Ethics is engaged in discussions with counsel for other science-oriented agencies to explore criteria for waiving research grant "conflicts." Any criteria ultimately developed by this group will, of course, still need the OGE approval and then promulgation as regulations.

Quite obviously, adoption of any (b)(2) regulations is many months, and probably years, away. The process requires consultation, before any proposal is published in the *Federal Register*, between the OGE and the Office of Personnel Management, the Department of Justice, and the Office of Management and Budget. After publishing the proposal as a Notice of Proposed Rule-Making (NPRM), the OGE must allow for public comment, respond to this comment by changes in the proposal or justification of the proposed action, and proceed once again through the executive branch review process (OPM, Justice, OMB) to develop the final rule.

Subsection 208(b)(3)

Subsection (b)(3), the most significant of the waiver authorities, and of most immediate concern to the FDA and the IOM committee, applies specifically and exclusively to members of advisory committees. Under this provision, the appointing official is allowed to grant a waiver for a committee member, who would otherwise be disqualified from discussing a particular matter, i.e., a specific agenda item, to participate in deliberations *on that matter* without violating the law. "The exercise of this authority calls for a judgment in writing "that the need for the individual's services outweighs the potential for a conflict of interest created by the financial

interest involved." This exemption was added to the law in 1989 to facilitate the participation of members of expert advisory committees.

For an the FDA advisory committee, subsection (b)(3) requires a judgment by the FDA Commissioner that the value of a committee member's participation outweighs the risk of conflict of interest posed by his or her financial interest. It provides the framework within which virtually all "waivers" for the FDA advisory committee members are processed. Subsection (b)(3) clearly calls for a context-specific judgment, one that takes into account not only the interest involved but the contribution that the member can make to the committee's deliberations on the matter before it. Thus, the law presumably allows an assessment of the member's expertise, familiarity with the issues, and uniqueness on the committee in light of the issues to be addressed. And exercise of the authority would seem to call for a personal judgment by the FDA Commissioner —or by the official to whom he delegated his authority.

The Commissioner's authority to grant waivers under (b)(3) is in addition to the authority to grant waivers under (b)(1) and, if the OGE regulations are ever promulgated, under (b)(2). Thus, if an the FDA advisory committee member qualified for a (b)(1) waiver or a categorical (b)(2) waiver, there would be no need to consider his/her eligibility to participate under (b)(3). On the other hand, this also means that a member who could *not* qualify for a waiver under (b)(1) or (b)(2), e.g., because his or her interest is too large or too likely to be affected, may still be eligible for a (b)(3) waiver based on his or her importance to the committee's deliberations. The FDA Commissioner's authority to grant waivers under subsections (b)(1) and (b)(3) is, under DHHS policies, subject to review by the Office of the Special Counsel for Ethics (OSCE); his authority under the Executive Order requires consultation with the OGE.

Thus, the impact of this legal regime on the FDA advisory committee members, and on the advisory committee system, will be a function of three factors: (1) the types of interests held to fall under the prohibition of section 208 (a); (2) the kind and number of relationships that advisory committee members (*and their family members and employers*) have with manufacturers of the FDA-regulated products; and (3) the specific issues on which the FDA seeks committee advice. Importantly, for this study, each of these factors has been undergoing change.

It is important to emphasize that 18 U.S.C. §208 is a criminal statute whose violation carries criminal penalties and whose enforcement involves criminal investigation procedures. Accordingly, it is entirely appropriate for the FDA and the DHHS to take seriously their obligations to protect both the agency's decisional process and the members of advisory committees from committing violations.

The granting of a waiver must be understood in this context. What is being waived by the agency is not an individual's conflict (or potential conflict); a waiver is an acknowledgement of a conflict. Instead, what is being waived is the criminal liability of the advisory committee member that would attach to participation with a prohibited interest. Seen in this light, the system has an obvious justification. Some committee members who have complained about the intrusiveness of the agency's questions or delays in approval of their appointments or their participation, may not have fully appreciated the importance of the exercise in protecting them as well as the agency.

FDA'S ADMINISTRATION OF CONFLICT-OF-INTEREST RESTRICTIONS

Federal conflict-of-interest laws impinge on the FDA advisory committee operations at two stages, each of which has multiple steps. The first stage is when an individual scientist or clinician is being considered for initial appointment and involves screening prospective committee members for potential conflicts of interest. It is this point at which most of the information about and individual's personal, family, and employer or institutional financial interests is sought and provided. The identification of potential conflicts of interest, however, does not result in rejection of many candidates at this stage simply because the specific issues on which their advice will be sought are not generally known.

The conflict-of-interest laws do not forbid the FDA to appoint as advisory committee members individuals who have financial relationships with the FDA-regulated firms. They do forbid the participation of a committee member in a "particular matter" in which he or she has a financial interest. Thus, a judgment of whether the law applies can only be made by considering, in the case of advisory committee members, the specific agenda items on which their advice will be sought. Each committee agenda item, therefore, presents an occasion for evaluating a member's potential conflict-of-interest.

Consequently, agency and departmental administration of conflict-of-interest laws focuses on the second stage, when meeting agendas are known and the "particular matters" to come before the committee have been identified. This stage involves identifying potential conflicts and determining when to seek waivers, preparation of waivers, and processing waivers.

Screening Potential Committee Members

The recruitment, nomination, and appointment of the FDA advisory committee members has been described in Chapter 5. This section focuses on the stage at which the FDA seeks to identify a prospective member's potential financial interests and thereby equip itself to monitor compliance with section 208.

Once a nominee for committee membership has been tentatively approved at the center level, a member of the FDA staff, usually the committee executive secretary or a member of the advisory committee management staff, contacts the individual by telephone to determine his or her availability and to identify any factors that might preclude appointment or diminish the individual's effectiveness. In all three centers, this initial conversation also includes "prescreening" questions that solicit information about the nominee's financial interests and relationships. The purpose is to discover future potential conflicts of interest. At the time of this study, the prescreening forms being used were several years old and did not elicit information about spousal or employer financial interests.

Although the FDA has no formal threshold, an advisory committee nominee at this initial stage may be judged to have so many attachments to the drug, biologics, or device industries that the appointment should not be made. The rationale is that numerous potential conflicts will limit the individual's ability to participate in committee discussions. Occasionally a potential member is ruled out because his or her attachments to industry are simply too great to pass an "appearances" test, even though they might not require frequent disqualifications. Any decision not to pursue recruitment of a prospective committee member because of excessive potential conflicts is taken with the concurrence of the division or office director.

Following this preliminary screening of a prospective committee member, he/she is sent an "appointment package" that solicits more specific professional and financial information. Although the appointment packages sent by the three centers differ in small details, they are roughly equivalent. Of particular interest is Form 2637—the Confidential Statement of Employment and Financial Interests. Form 2637 seeks information about financial holdings or business arrangements with *any* firm, regardless of whether it is known to be regulated by the FDA, as well as employment by and/or consultantships with FDA-regulated firms. (Current instructions for completing the form do not clearly specify that the SGE should include the financial interests of his or her spouse, minor children, partner, and any organization in which he/she serves as officer, director, trustee, general partner or employee, and of any person or organization with whom he/she is negotiating or has any arrangement for prospective employment.) The

prospective advisory committee member returns the completed appointment package, including Form 2637 and a current curriculum vitae.

Upon receiving the appointment package from the potential member, the center staff prepares a nomination package that is sent to the Committee Management Office within the Office of the Commissioner. The Committee Management Office serves as the liaison between the centers and the Commissioner's office and between the FDA and the DHHS. At the same time, relying on Form 2637, an SGE program officer within the center prepares a list of exclusions, i.e., a list of companies, products, members, or topics the discussion of which the member may not participate in because of a potential conflict of interest under section 208 (a). These exclusions, which are listed on a (HHS) Form 410 and hence are referred to as "410 exclusions," are generated by comparing Form 2637 against a now-outdated database of FDA-regulated companies supplied by the FDA's Division of Ethics and Program Integrity (DEPI) and supplemented by further investigations by the SGE program officers. Copies of this "410 exclusions" list and the completed Form 2637 are then returned to the new committee member and are also sent to the division director responsible for the committee and to the DEPI.

The initial decision to appoint committee members is largely the responsibility of the division and or center responsible for the committee. the FDA's Office of Chief Counsel is rarely involved. The Commissioner's office usually plays only a formal role in committee appointments. Beyond signing the appointment package, the Commissioner himself is seldom involved. No DHHS conflict-of-interest review is carried out at this stage. Nor does the OGE have a role in the initial appointment process.

As a result, the FDA officials exercise significant discretion about the magnitude and type of financial interests or relationships that should be considered wholly disqualifying. the FDA Staff Manual Guide, Section 3118.2, part 6, provides general instructions for the screening of individuals for potential financial conflicts, but it offers no concrete guidance regarding acceptable types or magnitudes of financial relationships.

The usual results of the FDA's "financial interest review" at the appointment stage are, first, to confirm the nomination, and second, to create a record of the member's potentially disqualifying financial interests. The latter provides the information on which a determination will be based either to disqualify from participation or to seek a waiver when a specific meeting agenda gives rise to a potential conflict.

Identification of Conflict and Decision to Seek a Waiver

The process for review of conflict-of-interest compliance begins with the effort to identify advisory committee members who may have a potential conflict with respect to one or more matters scheduled for discussion at a committee meeting. To identify such individuals, the center's SGE program officer obtains from each executive secretary: (1) a tentative agenda, usually taken from the *Federal Register* announcement of a meeting, as well as any additional topical information supplied by the executive secretary; (2) the names of company sponsors of products scheduled for review; (3) the products to be discussed and any closely competing products; and (4) a list of other issues to be discussed.

To maintain a current record of the financial/employment relationships of committee members, before each meeting the SGE program officer sends an update form to each member. This and the original Form 2637 completed by a member are the basis on which exclusions are identified. The SGE program officer determines which, if any, committee members are presumptively excluded from a matter scheduled for discussion at the upcoming meeting. An exclusion requires disqualification from that matter unless a waiver is sought and approved.

The SGE program officer, the executive secretary, the division director, and the office director may all be involved in deciding whether to seek a waiver for a committee member who has an exclusion. This decision is ostensibly based on the need for the individual member's expertise and potential contribution to the planned discussion. However, the importance of assuring a quorum at the meeting is also often a factor in assessing the need for a member's involvement. For a committee member who has only a few exclusions, the decision to seek a waiver appears to be almost automatic.

A RAPIDLY CHANGING SYSTEM

Throughout the 1980s the system for identifying potential conflicts of advisory committee members and, in appropriate cases, processing waivers (generally based on subsection (b)(1) of the law) was internal to the FDA. It also appears to have escaped close oversight by the Commissioner's office and there was rarely any legal review of waiver decisions. The system ran smoothly, if in retrospect somewhat unprofessionally.

But later events revealed that the insulation from high-level administrative and legal oversight had resulted in neglect at both the center level—where necessary information about committee member interest was often not solicited —and at headquarters—which continued to adhere to outdated

internal guidelines. Importantly, the responsible the FDA units, for some period of time, ignored, perhaps unknowingly, the important changes Congress made in the conflict-of-interest law in 1989. Absent legal guidance, they continued to operate on procedures based on the now-outdated pre-1989 law. Specifically, they did not modify the procedures regarding the eligibility of advisory committee members for subsection 208(b) waivers.

This system began to come under mounting stress in 1991, shortly after Dr. Kessler was appointed Commissioner of Food and Drugs. Kessler came to the FDA with a commitment to restore the agency's integrity, on the heels of a scandal involving generic drug approvals. He also professed a commitment to seek the advice of the nation's best scientists and supported the FDA's long reliance on expert advisory committees.

Notable Controversies

In the latter half of 1991, however, the agency brought before several different advisory committees a series of high-profile and deeply controversial issues involving, for example, the approvability of a new drug for Alzheimer's disease, the continued marketing of silicon-gel breast implants, and the alleged suicide-inducing properties of the nation's best-selling antidepressant. These meetings brought the conflict of interest of the FDA advisory committee members, and the agency's system for controlling it, under unprecedented scrutiny.

The scrutiny occurred partly because the FDA officials themselves realized that the controversial nature of the issues required that the agency take precautions to assure committee integrity. Even so, outside parties who were disappointed by the agency's decisions often challenged the objectivity of advisory committee members. the FDA's criteria and procedures for identifying potential financial conflicts and processing waivers caught the attention not only of the Commissioner and his advisers but of other officials inside and outside the agency.

Scrutiny was also heightened because these controversial cases occurred in a very compressed period of time, from late 1991 through mid-1992. In many ways, they were unrelated to each other in substance. But the cumulative effect produced by their rapid, sequential occurrence was substantially greater than it would have been if they had been spaced over a longer period.

The events of 1991 and 1992 exposed the dimensions of the conflict-of-interest "problem" on which Dr. Kessler urgently sought the IOM Committee's guidance. Accordingly, we provide a chronological account of these advisory committee meetings.

Psychopharmaceutical Drugs Advisory Committee: Meeting of September20, 1991

This meeting was called to discuss an increased number of reports of adverse reactions linking use of the drug Prozac (fluoxetine), manufactured by Eli Lilly, and other antidepressants to suicidal ideation in clinically depressed persons. The objective was to consider the adverse reaction data to determine the existence of causality between these drugs and suicidal or other violent behavior. Although it was apparently not the FDA's plan to invite discussion of specific product submissions or to solicit advice on remedial actions that would impact manufacturers of Prozac or other antidepressant drugs, the agency realized that the committee could potentially recommend action that might bear on the use of these drugs.

Accordingly, because the advisory committee might recommend actions that could affect manufacturers of antidepressants, CDER's Office of Consultants and Advisors decided to request waivers for all committee members who reported any financial interest with any manufacturer of antidepressant drugs. Therefore, waivers were sought for four members and two consultants who were found to have an exclusion(s).

The exclusions for the members were:

- Member #1: The member was involved in Merck's Phase IV study of the clinical safety and efficacy of a new neuroleptic drug (remoxipride). The study was funded at $95,000 for the period from February 1991 to January 1992. The member received no personal remuneration from the study.
- Member #2: The member was the principal investigator under a grant from Sandoz to study HLA phenotypes and vulnerability to Clozapine-induced agranulocytosis. The grant covered the period from September 1988 to January 1999. The hospital that employed the committee member was named as the grant recipient of $65,790. In addition, the member gives Sandoz-sponsored lectures on an ad hoc basis at various professional societies and medical institutions and is paid for these by Sandoz.
- Member #3: The member had a reported financial interest in Bristol Myers Squibb because his or her spouse is employed by this firm.
- Member #4: The member's employer, an academic institution, had various research grants with antidepressant manufacturers. These included: (1) a grant of approximately $100,000 from A. H. Robins for which the member was a co-investigator on a study of Zacoprid; (2) a grant of approximately $100,000 from Wyeth-Ayerst for which the member was the principal investigator (PI) on the study of Zalosperone;

(3) two pending studies to be funded at $100,000 each from Eli Lilly, the makers of Prozac, one dealing with depressants and the other with sexual dysfunction; (4) a grant of approximately $100,000 from SmithKline Beecham for which the member was the PI on a study of Paroxetine; (5) a grant of approximately $100,000 from Pfizer for which the member was the PI on a study of Tandosperone; and (6) a grant of approximately $100,000 from Ciba-Geigy for which the member was the PI in an ongoing research study of antidepressant drugs.

The FDA process for generating waivers for this meeting differed from the practice that has recently evolved. The identification of exclusions, the need for a waiver, the sufficiency of the documentation justifying a waiver, and the approval of the waiver were handled entirely within the FDA. The following steps were involved:

1. Exclusions were identified for committee members and consultants the week of September 12, 1991.
2. (b)(1) waivers requests were initiated the week of September 12–17.
3. The DEPI signed off on the request for (b)(1) waivers on September 17, 1991.
4. At the time of the meeting, the CDER Director had approved waivers for members and consultants with the concurrence of the Associate Commissioner for Management.
5. The committee meeting was held on September 20, 1991.

Three days after the meeting, on September 23, 1991, the Citizen's Commission on Human Rights wrote to the FDA alleging that certain members of the committee had conflicts of interest. Their specific charge was that a number of individuals on the committee as well as several consultants to the committee had interests in companies that manufacture antidepressant drugs or were conflicted with respect to the "psychiatric industry" because they were psychiatrists.

In reply to these charges, the FDA noted that 18 USC §208(b)(1) permits waivers when the appointing authority certifies that the "interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect from such ... employee." At the time of the September 1991 meeting, the FDA program staffs were operating under the old conflict-of-interest statutes, ignoring subsection (b)(3), which had been added to the law by the Ethics Reform Act of 1989.

The facts that the waiver process operated without legal oversight and was oblivious to the latest changes in the conflict-of-interest law suggested that the process was in severe need of scrutiny. The reliance on subsection

(b)(1), instead of the more liberal (b)(3), seemed difficult to reconcile with the members' and consultants' interests as described above.

General and Plastic Surgery Devices Advisory Panel: Meeting of November12–13, 1991

The purpose of the meeting of November 12–13, 1991 was to review seven premarket approval applications from manufacturers of silicone-gel breast implants. The agency wished to elicit recommendations regarding the continued marketability of these devices.

Twenty voting members and consultants were to attend the November 12–13, 1991, committee meeting. The program staff identified three voting members and two consultants who had exclusions with respect to matters that would be discussed.

- Members #1–3: Three members were practicing plastic surgeons who were members of the American Society of Plastic and Reconstructive Surgeons, Inc. Since the Society has assessed its membership approximately $4 million to counteract the negative publicity on breast implants generated by the FDA meeting and the media, the center decided that the plastic surgeons had a potential conflict of interest. Consequently, (b)(1) waivers were sought for these individuals, but not for full participation; rather they were to be allowed to participate in the discussion as nonvoting consultants.
- Consultants #1 and 2: Two consultants to CDRH had indicated that they had served as "expert witnesses" in cases involving women allegedly injured by silicone breast implants. Waivers were sought to allow them to participate in the meeting as nonvoting consultants.

The waiver process for the November 1991 meeting involved two "new" layers of review. Given the expected public attention to this meeting, the CDRH took great care in choosing members and solicited legal advice from the FDA's Chief Counsel's Office, which had not previously been involved. In addition, the Office of the Special Counsel for Ethics (OSCE) became involved in these discussions and, for the first time, reviewed the proposed waivers for legal sufficiency. The waiver review and approval process now included the CDRH, the DEPI, the FDA Chief Counsel's Office, the Commissioner, and the OSCE for the department.

The agency was well aware that the subject of silicone breast implants was attracting intense public scruity. In an unusual move, the CDRH scheduled over 100 interested parties to give testimony in the open public session of the meeting. The meeting was covered and reported by

newspapers, television, and the trade press. Committee members sat through the meeting facing television cameras and Kleig lights.

Meeting arrangements provoked sharp negative reactions from the members of the advisory committee. The regular chair of the GPS Devices Panel, Dr. G. Warden, a male, was replaced for this meeting (and for a February 1992 follow-on meeting) by the female chair of the OB-GYN Devices Panel. One apparent reason for this was to assure prominent representation by females. As a direct result of these two meetings, Dr. Warden resigned from the committee. In a highly publicized move before the February meeting, the FDA stripped the vote from another standing panel member because of statements given to the mass media, which prompted the agency to question whether he could render, or would be seen as capable of rendering, objective advice.

Arthritis Drugs Advisory Committee: Meeting of December 6, 1991

The purpose of this meeting was to discuss the Therakos NDA for a combination drug-device treatment of scleroderma using methoxypsoralen in conjunction with photopheresis. The NDA involved the drug, since the device had previously been approved for a related application. This application attracted considerable attention because the drug's sponsor and its clinical investigators charged that the FDA had mishandled the review. The House Subcommittee on Oversight and Investigations of the Energy and Commerce Committee later held a very critical hearing on the issue and has taken a continuing interest in the episode.

The salient conflict-of-interest issues involved CDER's decision not to seek a waiver for a consultant who was (later) alleged to have a conflict of interest. A description of the events of this situation follows.

After his term expired, the former chair of CDER's Arthritis Drugs Advisory Committee continued as a consultant to the Pilot Drug Evaluation Staff. In that capacity he served as the primary clinical reviewer of the methoxysporalen/photophoresis NDA mentioned above. At the same time, he was involved in preliminary negotiations to participate in a study of D-penicillamine, an alternative therapy for treatment of scleroderma. This study was funded by the FDA's Office of Orphan Drugs. The consultant was to serve as principal investigator at one of several centers participating in a multicenter trial. The grant for the D-penicillamine study would not have been made directly to the consultant's employer, a university, but to another organization. The consultant would have received no compensation from the grant.

CDER decided not to seek a waiver for the consultant because it concluded that, under prevailing the FDA policy, he had no conflict of interest. This decision was not subject to any legal oversight. The consultant had no financial interest in the D-penicillamine study, or in the company that manufactured it, or in any competing firm. All funding for the proposed study would have been supplied by the FDA.

Subsequently, Therakos and its clinical investigators charged that the consultant had been biased against the methoxypsoralen/photophoresis application because he was likely to be involved in research on a rival therapy. Their claim was that if the Therakos application had been approved, the consultant's own research would have been threatened. The allegation precipitated an investigation by the DHHS Office of Inspector General into possible violations of the law.

In this case, the FDA's policies failed to protect its consultant from a criminal investigation. Beyond the personal tribulations of the consultant, many such incidents would surely impair the agency's ability to attract capable clinicians/researchers to serve on its advisory committees.

Blood Products Advisory Committee Meeting: December 12–13, 1991

The purpose of the meeting was to discuss a Product License Agreement (PLA) for two recombinant factor VIII products. The sponsors of the PLAs were Baxter Healthcare/Hyland Division and Genetics Institute, its development partner, and Miles Laboratories, a division of Bayer, A.G.

Three committee members were excluded for specific portions of the meeting:

- Member #1: This member was the principal investigator on a study of Baxter's recombinant factor VIII product. In addition, as a consultant to Baxter he occasionally lectured about the VIII product, for which he received an honorarium and travel expenses. CBER's Division of Transfusion Sciences did not request a waiver for this member.
- Members #2 and 3: These members had an (unspecified) interest in the Genetics Institute. Accordingly, the Division excluded them from discussion of the Baxter product. No waivers were sought for the other parts of the meeting, in which they participated.

This reveals a heightened sensitivity to conflict of interest within the FDA. Largely because of this increased sensitivity, the CBER division elected not to seek waivers for the three committee members. However, due to a miscommunication within the program staff, Member #1 was not

informed of his exclusion until the day before the committee meeting. Believing that his participation in Baxter studies should not have disqualified him from participation in the discussion, the member vigorously protested to the Commissioner.

Biologics Response Modifiers Advisory Committee: Meeting of January 16–17, 1992

The purpose of this meeting was to review two PLAs: (1) Proleukin (Interleukin2), made by Cetus/Hoffman LaRoche, and (2) Oncoscint, made by Cytogen. Two committee members, one of them the chair, had exclusions for the Proleukin discussion due to their consulting activities with Hoffman La Roche.

By the time of this meeting, the FDA's system for processing waivers had expanded to included this CBER program area, the DEPI, the FDA Chief Counsel's Office, the DHHS Office of Special Counsel, the Office of Government Ethics, and finally, the Center Director's Office. The process had become both contentious and time consuming. The late discovery of a business relationship between Cetus and Hoffman La Roche triggered an eleventh-hour reevaluation of the members' interests. The chronology in this case follows:

1. Exclusions were identified by CBER committee management staff on January 13, 1992, 4:00 p.m., for an advisory meeting scheduled for the 16th.
2. Waiver requests were initiated by CBER committee management staff for two members on January 14.
3. Because of the scheduled meeting date, the waiver requests were faxed simultaneously on the 14th to the DEPI, the FDA Chief Counsel's Office, and the Office of the Special Counsel for Ethics. Telephone conference calls were held that day to expedite the process. The Chief Counsel's Office sought additional details of the financial interests of the two members.
4. On January 15, uncomfortable with the "appearance of a rush" in getting the waivers approved, the DHHS Special Counsel offered a compromise. The two committee members could be granted waivers to participate and vote, but the chair of the committee would, in exchange, be required to relinquish the chairmanship for this portion of the meeting. Acceding to this "compromise," the CBER committee management staff asked the committee chair to step down for the discussion of the Cetus PLA.

5. The CBER Director signed the waiver requests on January 16, just a few hours before the meeting was scheduled to begin.

This case illustrates several problems. First, the waiver process had become too cumbersome to cope with the last minute "discovery" of financial connections. Given the complex relationships between companies, such last minute discoveries may not be an infrequent occurrence. Second, program offices and legal reviewers displayed no inclination to cooperate, leaving both feelings of distrust and frustration. Third, the legal basis for conditioning the chair's full waiver on his acceptance of a diminished role is unclear.

Dermatologic Drugs Advisory Committee: Meeting of April 10, 1992

We believe this committee meeting was one of the first instances in which waivers for interests held by employers (university or other institutions) of committee members were required. In an April 6, 1992, memorandum to the CDER committee management office, the DEPI advised: "An additional concern is the requirement under (sub)section 208(a) that the financial interests of an SGE's employer, and other affiliations be considered, and must be addressed in the waiver. The potential impact of these entities has not always been considered in waivers which were requested prior to February, 1992. Therefore, under the new requirements each waiver request must address these concerns, before they are forwarded to the OSCE. We have learned that the Office of Government Ethics plans to draft a class waiver for all university affiliations. Until this class waiver has been approved, each 18 U.S.C. 208 waiver must address the SGE's university affiliations." This was the first written notice that the centers received regarding this change in policy.

Consequently, on April 9, one day before the scheduled Dermatologic Committee meeting, the CDER committee management office was faced with the task of preparing 11 (b)(3) waivers for members who were employed by universities. The waivers were signed by the center Director and DEPI on the 9th, and were delivered to the Commissioner's Office the next morning for his signature.

The requirement of waivers for university affiliations greatly affected the center's workload. Since most advisory committee members are affiliated with universities, whose hospitals dispense products manufactured by various companies with applications before the FDA, from this point on nearly every member required a waiver to participate. By the end of June, such waivers accounted for roughly two-thirds of all waiver activity within CDER.

Circulatory Systems Devices Panel: Meeting of May 11, 1992

The purpose of the meeting was to review a PMA for a coronary atherectomy system. This case is a dramatic illustration of how miscommunication among the offices involved in the waiver process delayed consideration of a small manufacturer's application, probably with severe financial consequences for the company. The events leading up to the meeting are:

1. In early March 1992, the CDRH program management office was notified of a panel meeting scheduled for May 11.
2. On March 13, exclusions were identified by the committee management office, and on that basis, 13 (!) waivers requests (for 8 members and 5 consultants) were prepared. One of the requested waivers was for a member who had been designated as the lead reviewer for the atherectomy catheter PMA. The presumptive "conflict" for this member was that his institution was involved in the coordination a large-scale randomized trial evaluating coronary atherectomy versus balloon angioplasty (known as the CAVEAT Trial). This trial, funded by Devices for Vascular Intervention and Eli Lilly in a grant for $2.3 million, is a prospective clinical trial involving 35 clinical sites throughout the United States and Europe.
3. On March 24, the sponsoring companies were notified that their applications would be reviewed on May 11. The notice of the meeting was published in the *Federal Register* on April 20.
4. By April 21, waivers had not been approved for many panel members. The CDRH Division of Cardiovascular, Respiratory and Neurological Devices informed the committee management office that the meeting might have to be cancelled if the requested waivers were not approved by April 24.
5. On April 24, the center's committee management office conveyed verbal clearance to the program area, which permitted mailing of all meeting material to committee members for review.
6. On Friday, May 8, CDRH's committee management office was informed by the DHHS Office of the Special Counsel for Ethics that no waiver would be allowed for the member who had been assigned as lead reviewer for the atherectomy catheter. Unsuccessful attempts were made to reverse the decision and a final refusal to grant a waiver was received at 3:45 p.m. The center decided to cancel the review of the atherectomy catheter PMA due to the inability to find a substitute reviewer over the weekend before the Monday meeting.

7. Late on Friday, the sponsor of the PMA and the committee members were notified of this change in the agenda. The sponsor was outraged and threatened to take all measures possible to "exact compensation" for the delay.
8. On Saturday, the Commissioner's office contacted the sponsor to allow it to present its application to the committee. An attempt was made to notify committee members of this change in agenda, but most could not be reached.
9. At the committee meeting on Monday, May 11, the members were told that the PMA had been restored to the agenda. The chair polled the members to determine whether they felt comfortable proceeding with the review. All of the members felt that they were inadequately prepared and voted unanimously to postpone review of the application.

The problems evident in this case speak for themselves. The reviewing division apparently assumed that the lead reviewer's presumptive conflict was waiverable. However, the Special Counsel for Ethics Office, exercising independent judgment, determined that his involvement in research on a competing technology precluded a waiver. This judgment was communicated only at the eleventh hour, disrupting the committee meeting and frustrating the sponsor's hopes for product development. The issue of waivers for committee members involved in research on competing technologies still presents problems for the FDA.

The preceding cases illustrate several of the confusing and frustrating events that have occurred within the centers' respective committee management offices between the period from September 1991 and June 1992. The rapidly escalating scrutiny of potential conflicts, the number of parties involved in the waiver process, the expanding criteria for identifying potential conflicts, and the zeal with which these criteria were applied combined to wreak havoc in the FDA's advisory committee operations.

Analysis of Waiver Processing

To fully appreciate the impact of these events, it is instructive to look at the waiver process that the centers followed during this period. Before the fall of 1991, the waiver drafting and review process was entirely internal to the agency. The centers (committee management staff) decided when a waiver was necessary and wrote the justification for the waiver. DEPI reviewed the waiver justification and usually recommended its approval without change. Waivers were approved by the authority of the center director with the concurrence of the Associate Commissioner for Management. There was no legal oversight of this process.

By the end of June 1992, drafting and review of waivers had become a much more arduous process. Each waiver must now state the precise exclusions for which the member is being waived as well as providing a clear explanation of the "need" for the individual's participation. In current waivers the exclusions are listed in extreme detail; e.g. what percentage of the individual's income is represented by a particular financial interest. Additionally, the "need for the member" portion of the waiver is being reviewed more critically; in the past, statements to the effect that a member was a preeminent scientist and a member of the committee generally sufficed as a rationale.

A very serious flaw in the current waiver process is the lack of relevant written standards, at any level, for granting waivers, i.e., for ranking potential conflicts, for deciding whether a member's importance outweighs any risk of conflict, or for explaining decisions to grant (or deny) waivers. This has resulted in a customized, time-and resource-consuming process of case-by-case discovery and rationalization. Not infrequently, the process leads to burdensome iterations; one new discovery raises several more questions about other possible financial connections, requiring that the committee member be contacted again and asked to provide more information.

A likely, but hard to quantify, cost of this system is the disillusionment, and perhaps ultimate withdrawal, of advisory committee members who resent the disclosure of personal financial information, the repetitious requests for more information and clarification, the eleventh-hour decision about their eligibility (or disqualification) for participation, and the residual innuendo that they cannot be trusted.

Another consequence of the lack of written standards for approving waivers is that the process often becomes a hurried, sometimes frantic, rush to complete the waiver request just before an advisory committee meeting is scheduled to begin. This frustrates all participants. The FDA staff responsible for initiating waiver requests are most frustrated because they view the process as obstructing program goals and because decisions get made late, often long after their involvement, and without clear explanation. Those near the end of the process display less frustration, save with those who initiate waiver requests, because they have very different program objectives, such as preservation of department- or government-wide uniformity, avoidance of embarrassment for the administration, and maintenance of decisional integrity.

Even if one examines a number of prior decisions, as we have done, the current operational criteria for approving a waiver are elusive. The statute requires a judgment, ostensibly by the Commissioner, that a committee member's participation in a particular agenda item is important enough to justify the potential conflict. Recently, this decision has been made at the

level of the OSCE or the OGE and the OSCE, several levels removed from responsible authority.

On the other hand, the participation of these offices in the waiver process has introduced a level of legal rigor that was lacking in the pre-1991 process. The desire to conform existing practices to the 1989 law is commendable given the stakes involved, although the zeal with which this task has been approached may have obscured the need to fashion an orderly and predictable system for determining whether waivers are needed and justified.

The OSCE and the OGE, based on guidance from the Department of Justice, have interpreted Section 208 as reaching a very wide range of interests. The statute has been interpreted as embracing nearly all personal, spousal, minor child, and employer financial relationships, regardless of size, as presumptively disqualifying. For example, a member's employer may have a financial relationship with the company whose submission will be the subject of the committee meeting. Because there is no threshold limit on the size or remoteness of such employer connections, the practical outcome is that every member who is employed by a university whose hospital dispenses drugs made by the manufacturer whose submission is under review requires a waiver. Similarly, waivers are required for members whose institution may own stock in, or received an endowed chair from, the manufacturer.

The reach of the law has also spread with imaginative analysis into the matter of competing products and technologies. The OSCE has taken the position that a member with a connection, e.g., a research grant, with a company that is developing a technology that could be substituted for the product before his or her committee will require a waiver to participate. Rigorous implementation of this theory means, for example, that if a device pending approval will be offered to treat the same condition as an existing drug, members of the device panel must be screened for their, their spouse's, and their employer's financial relationship with the maker(s) of those drugs.

The OSCE and the OGE have also displayed concern about "appearances" of conflict of interest. In the proposed regulations (56 FR 33778) that followed Executive Orders 12674 and 12731 and the Ethics Reform Act of 1989, the OGE announced that even employees (including SGEs) who would not violate the law if they participated may nonetheless be disqualified from participating because of an *apparent* conflict. Usually, concerns about appearances of conflict surface in connection with high-profile advisory committee meetings in which potential press coverage may cause the OSCE to be more cautious than usual. In some such cases, the OSCE has insisted on "restricted" waivers: i.e., waivers that limit the member's participation in some way, typically by excluding the member from voting on a particular matter. The OSCE has argued that appearances of conflict

demand an "appearance solution" and, further, that restricting the participation of members with an appearance of conflict will reduce the chances for an actual conflict of interest.

Interpretation

The foregoing picture of the system managing potential financial conflicts of interest by members of the FDA advisory committees vividly reveals why Commissioner Kessler reported to the IOM committee that the agency faced a serious problem. It would be easy to assign blame for the emergence of the problem—to the divisions and centers for failing to appreciate the sensitivity of potential conflicts and viewing waivers as a matter of routine; to the DEPI for adhering to outdated policies and failing to appreciate the requirements (and perhaps even the enactment) of subsection (b)(3); to lawyers in the Office of the Chief Counsel for failing to provide either the centers or DEPI systematic legal guidance; to the Office of the Special Counsel for Ethics for excessive conservatism and failing to develop and convey general standards for approving waivers; to the Office of Government Ethics for last-minute and often unexplained second-guessing of waivers on which it was consulted; and to every level of the process for indifference to any reasonable set of deadlines for the development and approval of waivers.

There is, however, an alternative, less critical account. It is a story of offices and agencies caught suddenly in a confluence of forces that were moving too rapidly for any one to step back from the cascade of individual waiver cases to explain what was occurring and decide how the system should be righted. These forces included the heightened concern, within the administration and in Congress, over conflicts of interest involving federal employees; President Bush's decision to centralize in the OGE oversight of the waiver process for the entire government; Secretary Sullivan's decision to create a Special Counsel for Ethics responsible for reviewing all waivers granted within the department; the ripple effects of Dr. Kessler's own demands that the FDA officials and procedures should be, and should be seen to be, free from any hint of conflict of interest; a revived appreciation that the carelessness in identifying conflicts and granting waivers might not only jeopardize agency decisions but leave committee members exposed to criminal prosecution; and the reintroduction of lawyers, who were themselves confronting issues for the first time, into a system that had previously displayed an amateur understanding of the law. Under the circumstances, it is hardly surprising that confusion, acrimony, and frustration resulted.

Glimmers of Progress

As the IOM committee completed its work, there were signs that the participants in this process had themselves come to appreciate the nature of the "problem" and had resolved—within the practical limits of current law and executive orders—to improve the system's operation. The most promising of these steps was a meeting held between Mary Pendergast, Senior Advisor to Commissioner Kessler, and Jack Kress, DHHS Special Counsel for Ethics. Representatives of all five the FDA centers, including the three whose committees are the subject of this report, were also in attendance. Based on individual accounts of the meeting, it is possible to sketch the broad outlines of the reforms tentatively agreed on.

Workload

OSCE representatives agreed to consider one-time waivers for advisory committee members whose disqualifying interest is that of their university or hospital in sales of medical products of a company with a product under review by the FDA. Such one-time waivers would allow the committee member to participate in all future committee meetings. Since over half of all (b)(3) waivers now sought by the centers are for employer interests of this sort, approval of one-time waivers should dramatically reduce the waiver workload.

Waiver Preparation and Review

The FDA's centers will remain responsible for the initial screening of advisory committee members, for determining whether a member confronts a potential conflict relative to an agenda item, for deciding whether to recommend a waiver to the Commissioner, for preparing waiver requests, and for obtaining information from committee members. The OSCE will have final authority for the agency and the department to determine whether a member's participation—absent a waiver—would violate the law, i.e., whether a potential conflict of interest exists. Authority to decide whether to grant a waiver will rest with the Commissioner or, at his choice, the Deputy Commissioner for Operations. This understanding represents a constructive clarification and allocation of responsibility between the Commissioner, who under the law is empowered to grant waivers, and the OSCE, which Secretary Sullivan has made responsible for assuring that the conflict-of-interest laws are complied with.

Within the FDA, waiver review and approval is to be expedited. Centers will forward recommended waivers to the OSCE at the same time they are

submitted to the DEPI. The DEPI will be given 48 hours to respond, and silence will be construed as acquiescence. Meanwhile, presumably, the OSCE lawyers may carry out their own review. This arrangement would appear to subordinate the role of the DEPI, as well as to expedite review, and we consider both to be sensible. With the OSCE able to provide authoritative legal review of the need for, and form of, any waiver, the FDA's concern that waivers should be granted judiciously and only when necessary to assure effective committee functioning can be fully protected by the Office of the Commissioner.

Schedule for Review of Waivers

Centers are to submit recommended waivers to the OSCE (and to the DEPI) at least two and preferably three weeks before the committee meeting. The OSCE has committed itself to review such recommendations promptly and to use its best efforts to complete all corrections at least three days before the meeting. Under this arrangement, the Deputy Commissioner should have all waiver recommendations, approved as to need and form by the OSCE, three days before the meeting, which should provide adequate time to exercise independent judgment and, if necessary, confer with the OSCE. Understandably, exceptions to this schedule may be needed for consultants invited to assist the committee at the eleventh hour.

Waiver Form

Waiver forms will be divided into two parts. Part I will be a straight forward recitation that the Commissioner or Deputy Commissioner has granted a waiver for a committee member to participate in the discussion of an agenda item with respect to which he/she would otherwise have a conflict. Part II will consist of a more detailed explanation of the circumstances that give rise to the potential conflict and the reasons why the center (and agency) concludes that the member's participation ought nonetheless to be approved.

The IOM Committee views this meeting, and the agreements reached, as a significant first step. Given Secretary Sullivan's decision to lodge conflict of interest oversight authority for the entire department in the OSCE, this office will inescapably have a central role in the FDA's administration of conflict of interest restrictions applicable to advisory committees. Accordingly, for any system to work effectively, it must have the support and active cooperation of both OSCE and the FDA. The agreement to grant one-time waivers for certain attenuated employer interests should cut the FDA's waiver caseload significantly, but there will remain a number

of individual cases—intersections between committee agendas and member exclusions—that will require sensitive judgment and active, timely cooperation between the FDA, including the centers, and the OSCE. Our recommendation below that the two organizations make an effort to agree on, and in some fashion codify, the criteria for evaluating waivers in these more difficult cases will demand a much greater commitment to cooperative policymaking than has been evident so far.

RECOMMENDATIONS ON FINANCIAL CONFLICT OF INTEREST

The IOM committee believes that it is essential that the members of technical advisory committees be impartial and objective and not compromised by financial conflicts of interest. To achieve these ends, the IOM committee has addressed the standards and procedures for controlling conflict of interest.

Any attempt to address the problem must deal with issues of law, of bureaucratic procedure, and of administration. The IOM committee considered reforms that would require new legislation and those that could be implemented within existing statutory authority.

Options Requiring Legislation

The IOM committee considered several options that would require new legislation. For example, a recent report to the Administrative Conference of the United States advocated a system under which there would be no disqualification of any advisory committee member for financial conflict of interest, but each member would be required to make full public disclosure of all financial dealings, holdings, and relationships.[1] This proposal differs from the current system in two ways. First, full public disclosure of all of each member's financial interests goes well beyond the present extensive disclosure to the FDA and public disclosure only of agenda-specific conflicts that may disqualify or constitute the basis for a waiver. Second, it holds that no interest would preclude a member from participating in committee deliberations.

The IOM committee concluded that the latter feature of the proposal was unacceptable. It would permit an advisory committee member to serve in instances in which his or her financial interests would constitute a clear conflict of interest and in which the remedy should be disqualification from participation. Such a system would undermine the appearance of objectivity of the committee's advice.

A second option would be a system that coupled full disclosure of all interests with a general rule barring participation by members with significant financial interests.

Although this proposal may contain the core of a promising reform of the system for regulating conflict of interest, the IOM committee did not explore fully its ramifications. The committee's judgment—confirmed by many we spoke to, including officials of the FDA, OSCE, the OGE—was that such a major legislative overhaul of this magnitude was simply not a possibility in the near term. Thus, given the FDA's pressing needs, our charge, and our timetable, it seemed imperative for the committee to turn to reforms that could be implemented within the existing statutory framework. However, this possibility is clearly a candidate for further study.

Options Available Within Existing Authority

What can be done under existing authority? Potentially a good deal, as the following recommendations suggest. Although the first and second recommendations below could be implemented by the FDA itself, the successful implementation of the other recommendations would require the active involvement of the Commissioner and his office, the collaboration of the OSCE, and at least the tolerance of the OGE.

A theoretical option for the FDA would be to avoid appointing advisory committee members as special government employees, thus circumventing the restrictions of the federal conflict-of-interest law. This solution has the notable disadvantage of attempting to define the problem away, hardly a way to instill confidence in the system. Moreover, new legislation might be needed to allow payment of members and sharing with them of trade secret information.

Second, the FDA itself could exercise greater care in the initial appointment of advisory committee members. It could demand even more information that would enable it to identify in advance potential members whose financial interests would clearly disqualify them for some committee meetings. On the other hand, because the interpretation of a prohibited interest is already extremely broad, and because potential conflicts cannot be identified before meeting agendas are set, vigorous pursuit of this approach might disqualify valuable members and produce no gain in integrity.

Third, the FDA, working with the OSCE, could formulate and codify criteria for granting 208(b)(3) waivers. The IOM committee believes that this is essential. Codification would be a lengthy process, but some mutual understanding of the grounds for justifying a waiver is badly needed. A checklist of variables should be formulated that includes: the size of the

interest; the character of the interest; the likelihood than an interest will be affected by agency action based on the committee's advice; and the actual importance of the member to the committee deliberations. Regarding the latter point, we believe that committee membership alone should not be taken automatically as a decision measure of a member's importance.

Of immediate importance is the need to clarify the criteria for dealing with potential conflicts arising from institutional or employer financial interests, research grants and contracts to committee members, and member involvement with competing products and technologies.* Most advisory committee members are university employees; most of their employers operate medical schools, hospitals, and hospital pharmacies. The OSCE, with the FDA, should develop clear criteria for dealing with waiver requests that arise because a committee member is affiliated with an institution that operates such subordinate entities, which in turn derive income from the dispensing of use of the FDA-regulated products. Most universities also own diversified endowment funds and it is common for some portion of these to be invested in pharmaceutical, biotechnology, or medical device securities. The OCSE, with the FDA, should clarify the criteria for dealing with these "employer interests" as well.

The IOM committee recommends that the FDA and the OSCE begin the process of codifying the criteria for granting 208(b)(3) waivers, especially with respect to employer interests, research grants and contracts, and competing products and technologies.

Fourth, the FDA has the authority to streamline its own internal policies and procedures for deciding when to seek waivers and how to prepare their justifications. The IOM committee believes that this also is essential. Responsibility for preparing the initial waiver request should reside with the division. The decision to request a waiver should be made by the center director. The IOM committee sees no need for independent review of this decision by the DEPI or by the FDA's Chief Counsel, so long as the OSCE continues to exercise an oversight role. Central agency review of waiver requests should be by a high-level policy official in the Office of the Commissioner.

The IOM committee recommends that the FDA streamline its policies and procedures for requesting and processing waivers. This clarification should fix the primary administrative responsibility for implementing

* The IOM committee notes with approval that initial steps along these lines were initiated in the Summer of 1992.

these changes at the level of the center directors while retaining final authority to approve waivers at the Commissioner's level (i.e., at the level of the appointing authority).

Fifth, the FDA should develop and adhere to strict schedules for processing waivers. It should present waiver requests to the OSCE no later than three weeks in advance of a meeting.* The Commissioner should seek agreement from the OSCE that it will review any proposed waiver within three days. The Commissioner, who has the ultimate responsibility for approving waivers, may even wish to establish default rules that penalize centers for failure to complete their part of the process in a timely way (e.g., the member is disqualified or the agenda item is postponed). This or other default rules should be designed to ensure an expeditious process and also to guarantee that at no time would an advisory committee member of questionable impartiality be allowed to participate on the committee.

The IOM committee recommends that the FDA, with the cooperation of the OSCE, adopt a policy of strict scheduling for processing waivers and that such a policy include default rules for late submission of waivers.

Sixth, the FDA must update its training of officials who have responsibility for implementing conflict-of-interest policies with respect to advisory committee members. Training programs should build around the substantive and procedural changes suggested above. Participation should be required of all the FDA professional staff who deal with advisory committee members.

The IOM committee recommends that the FDA develop a conflict-of-interest training program for all of its professional staff who deal with advisory committees. This program should be based on the policy and procedural changes suggested in this report.

Seventh, the FDA must also initiate and maintain a formal orientation program for advisory committee members. Individual members should clearly understand the laws that govern financial conflict-of-interest and the justifications for granting waivers. However, the IOM committee believes that guidance on conflict of interest should be part of a broader orientation

* The IOM committee notes that if the FDA adopts the recommendation for advance scheduling of advisory committee meetings proposed below and in Chapter 7, it may be possible to increase this period of time.

program (discussed below and at length in Chapter 8). This linkage is important because an exclusive focus on conflict of interest will necessarily emphasize the risk of criminal prosecution and the need for intensive inquiry into personal financial matters—an emphasis that would surely obscure the public service dimension of advisory committee membership.

The IOM committee recommends that the FDA develop an orientation program for its advisory committee members and that this program include explicit attention to conflict of interest in the context of a broader orientation to the public service aspects of advisory committee membership.

Eighth, the FDA and OSCE, on behalf of the department, should continue to press the OGE to issue government-wide general (b)(2) waiver regulations as soon as possible. This yet-to-be-exercised statutory authority is intended to remove certain classes of potential conflicts from a case-by-case determination. Employer financial interests and some research grants and contracts could be dealt with by such a rule.

The IOM committee recommends to the Office of Government Ethics that it develop and issue government-wide 208(b)(2) waiver rules as soon as possible. It further recommends that the FDA provide input to the scope of these rules and that the FDA and OSCE continue to impress on the OGE the urgent need for such rules.

Finally, the FDA, and the department, should seek the revision of Executive Order 12674, which requires case-by-case consultation with the OGE on all waiver requests.

The IOM committee recommends to the President that Executive Order 12674 be amended to remove from the OGE the responsibility for case-by-case review of advisory committee member waiver requests, that authority for such case-by-case review be delegated to the departments, and that the OGE be directed to focus on agencies' policies and procedures.

INTELLECTUAL BIAS

This chapter thus far has focused on the methods for protecting committee deliberations against just one threat to impartiality—the possibility that committee members will modify their advice because of the prospect of personal or employer financial gain or loss. This focus is justified because

the administration of the financial conflict-of-interest restrictions applicable even to short-term federal employees is the main source of the problem on which our advice was sought.

But the FDA needs to guard against another potential threat to advisory committee objectivity. As a recent series of articles in *Science* magazine recounts,[2,3,4,5] there is a growing concern about—and considerable publicity surrounding—the subtly and perhaps even overtly biasing effects on objectivity of a scientist's prior research and public positions, particularly positions taken in formal administrative or judicial proceedings.

For convenience we have termed this potential effect "intellectual bias," which is meant to distinguish the problem at hand from financial conflict of interest. Too frequently, we think, both members and observers of the scientific community apply the term "conflict of interest" to the problem of intellectual bias, which is more complex and elusive than the sorts of financial conflicts we have heretofore been discussing.

Making this distinction is particularly important in the present context, because the FDA (and its advisory committee members) are subject to a set of formal criminal restrictions that apply only to *financial* conflicts of interest. Section 208(a) says nothing about possible intellectual bias or prejudgment that is untainted by financial interest. A committee member may be incapable of entertaining a particular hypothesis, however convincing the evidence, but he or she does not violate section 208(a) by participating in committee deliberations on an issue to which the hypothesis' plausibility is crucial. By participating, however, he or she not only threatens the committee's capacity to render impartial and thus useful advice to the agency, he or she may in so doing thereby jeopardize the validity of any decision that the FDA may reach based on the advice it has heard.

What legal restrictions apply in this context is a matter of some uncertainty. It could be argued that a committee whose members include someone with a closed mind on an important issue is not "balanced" as the Federal Advisory Committee Act requires. Even if this were plausible, recent cases have cast doubt on the enforceability of the FACA's "balance" requirement. Furthermore, the FACA requirement of balance cannot be translated easily into operational safeguards against possible committee member intellectual bias. When a new committee is formed, or a new member is appointed to an existing committee, it is impossible to anticipate all of the issues or applications on which the FDA will seek the committee's advice. The general jurisdiction of the committee will of course be known, but its future agenda cannot be. And it is possible bias with respect to a particular agenda item that the agency should be concerned about. Any practical approach to this problem must operate at the point that the

committee's agenda is set and the issues to be addressed at a specific meeting are determined.

The vulnerability of any decision reached by the Commissioner, the official decision-maker, is likely to be a function of his own rather than any committee's impartiality. The key factor seems to be whether the Commissioner's decision is required to be based on a formal adjudicatory record. Most of the decisions on which the FDA seeks advice from its committees do not require the agency to hold a formal adjudicatory hearing. Even so, it cannot be said with assurance that the participation of committee members whose views on crucial matters were already invariably formed might not provide a legal basis for setting aside the FDA's ultimate decision. Proving intellectual bias of such character would, of course, be difficult, and perhaps in all but clear cases, impossible.

Even assuming the risk of judicial reversal is small, however, there are very good reasons why the FDA should be concerned to assure that committee members are capable of maintaining an open mind in evaluating the theories and evidence brought before them. One is that a committee whose advice is not impartial defeats the very purpose of seeking independent expert advice. A second is that the widespread belief that some committee members are, if only rarely, immune to persuasion by evidence would surely erode public confidence in a mechanism the FDA has devised precisely to enhance confidence in its own decisions.

We do not consider intellectual bias to be a common problem among members of the FDA advisory committees. Scientists are trained to be skeptical, to insist on evidence to support hypotheses, and to be rigorous in their assessment of evidence. We are convinced the overwhelming majority succeed. Furthermore, the FDA advisory committee context probably presents fewer occasions for challenge to long-held views than many other contexts in which individual scientists are called on to offer their opinions. One reason is that advice-giving by a committee is a collective process and not an individual exercise.

However, it cannot be said that the FDA has no basis for concern about intellectual bias or no reason to take precautions to guard against it. The IOM committee believes that the agency should be sensitive to the possibility that, on particular issues, an advisory committee member might be so deeply committed to a point of view, or so publicly identified with that view, that his or her objectivity cannot be assumed or will not be credited by those who are interested in the committee's deliberations. What steps the FDA should take when such a case arises probably cannot be prescribed in advance; the appropriate remedy is likely to depend on the circumstances. Perhaps even more difficult is designing a formal system to screen for potential intellectual bias.

Remedies

Because no clear set of legal restrictions is operative here, the agency has a wider range of remedies from which to choose than it has under section 208. If the determination of bias rests on publicly stated positions, exclusion is probably warranted. There may be other cases in which this may also be appropriate, e.g., when a member is an inventor of the technology under review (even if he or she has no financial interest in its approval). And denial of participation surely would reduce the risk of recrimination and embarrassment.

There may, however, be instances in which exclusion of a member for possible bias would deprive the committee members who do participate of information helpful in their independent evaluation. If exclusion stems from the member's prior research, especially as a principal investigator, the FDA should not have to forego that individual's expertise. This can be solved by inviting the person to address the committee as a witness (or as a "guest"). In such an instance, it would be desirable to situate the individual so that he or she does not appear to occupy his usual role as a voting member of the committee.

On the other hand, there is some disadvantage to creating too large a set of roles at committee meetings to accommodate various perceived levels of partiality. A sensible rule of thumb might recognize just three roles for committee members in the case of intellectual bias: (a) full voting participation; (b) full exclusion from a meeting or an agenda item; or (c) appearance as "witness" or "guest" of the agency.

Short of complete exclusion, the success of any more limited remedy will depend on full public disclosure of the facts that give rise to the concern that the objectivity of an erstwhile committee member may be, or may be thought to be, in doubt. It may be possible to say that "Dr. Jones has agreed to recuse himself from the discussion of Product Y because of concerns that, based on prior work in the field, his objectivity may be challenged. He therefore will not participate in the committee's formulation of advice, nor will he vote. He has been asked by the FDA to be available as a witness to answer questions from voting committee members."

Screening

The development by the FDA of a system to screen for potential intellectual bias will require considerable thought. A member's prior research will probably be revealed in the screening for financial conflict of interest. All relevant publications presumably will be included in a potential member's curriculum vitae. However, it may be necessary for the agency to

inquire specifically about public positions, especially any taken before regulatory agencies or judicial proceedings.

This brief discussion barely penetrates the surface of a complex and very sensitive issue. It is sensitive, in part, because committee members whose objectivity might be challenged on other than financial grounds are often likely to resent the suggestion that they cannot be trusted. This is particularly true if the suggestion comes from the agency, which has appealed to their spirit of public service. Perhaps the heightened attention given to the subject within the scientific community will generate greater sensitivity on the part of individual committee members.

One further observation is in order. We consider the matter of intellectual bias to be a problem for the FDA to address and resolve. It is not covered by the federal conflict-of-interest laws and its possible occurrence is therefore not properly addressed through the formal waiver process. It obviously has legal ramifications to the extent that agency decisions might be subject to attack because of the participation of a committee member who lacked, or was accused of lacking, the requisite objectivity. But these are ramifications that the FDA's Chief Counsel is very capable of assessing and providing guidance on to the agency.

The IOM committee recommends that the FDA develop criteria and procedures for identifying potential intellectual bias of advisory committee members and protecting the objectivity and impartiality of advisory committees. The committee recommends that the agency routinely request information about research interests and publicly stated positions on scientific issues from advisory committee members. It recognizes that the agency must rely to a large extent on committee members themselves to provide such information.

When the agency concludes that a committee member has demonstrated a lack of objectivity on a matter, the member should be excluded from participation in the committee deliberations concerning that issue. If information reveals only the possibility of bias, the agency should determine whether to permit the member to participate. A member who is excluded from participation in committee deliberations might nevertheless be invited to offer views as a guest or witness called by the committee. Individual cases should be ruled on by the Commissioner, after consultation with the appropriate center director.

NOTES

1. Berg, Richard K., *Conflict-of-Interest Requirements for Federal Advisory Committees*, Report to the Administrative Conference of the United States (Washington, D.C., May 1989).

2. Barinaga, M. Confusion on the Cutting Edge. *Science* 257:616–619, 1992.

3. Marshall, E. When Does Intellectual Passion Become Conflict of Interest? *Science* 257:620–621, 1992.

4. Marshall, E. NSF Deals with Conflicts Every Day. *Science* 257:624, 1992.

5. Marshall, E. Intellectual Conflicts—Boon or Bust? *Science* 257:624, 1992.

APPENDIX

A Suggested Approach to the Codification of Section 208(b)(3) Waiver Criteria

SUPPLEMENTAL STATEMENT OF RICHARD A. MERRILL

The IOM committee recommends, appropriately in my view, that the FDA and the DHHS Office of the Special Counsel for Ethics (OSCE) "immediately begin the process of codifying the criteria for granting 208(b)(3) waivers, especially with respect to employer interests, research grants and contracts, and competing products and technologies." This statutory provision, specifically enacted for members of federal advisory committee, holds that an agency head may waive the potential financial conflicts of an advisory committee member if he determines that "the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved." It is this authority on which the FDA now exclusively relies in deciding whether to allow members with potential financial conflicts to participate in committee deliberations on a particular matter.

The IOM committee report itself does not offer concrete guidance on how this might be done. This apparent deficiency of the report becomes understandable when one grasps the difficulty of the exercise and recalls that the committee's schedule allowed for only four face-to-face meetings. Framing a discussion of which kinds of potential conflicts should be considered serious and which not, and of how to assess the importance of a single member to a committee's deliberations is a complex undertaking. Reaching judgments on these issues requires extended discussion and debate. There was scarcely time to attempt the first of these challenges, and no opportunity at all for the full committee to engage in the extended discussion needed to reach agreement on the second.

What follows is one member's attempt to outline the analysis he would follow in attempting to carry out the IOM committee's recommendation. It does not necessarily reflect, either in its approach or in the normative judgments implied, the views of any other committee member. It is offered to provoke further analysis within the FDA and OSCE rather than to prescribe a solution to the problem that they jointly confront.

The problem of codifying the criteria for approving waivers under 208(b)(3) is complicated by two main facts. First, the range of matters on which the FDA seeks advice from its advisory committees, when coupled

with the prominence and diverse activities of the members of these committees, generates a substantial number of presumptive "exclusions" that dictate nonparticipation or require consideration of waivers. An FDA committee meeting seldom occurs today without one or more members facing exclusion from one or more items on the agenda. In short, the agency faces a large "caseload" of potential waivers.

Second, the caseload is large in major part because the conflict-of-interest law, section 208(a), sweeps extremely broadly, embracing as potentially disqualifying of an individual committee member not only small personal (and family) financial interests but interests or relationships of the member's employer. As most committee members work for universities or other research and health-care providing institutions, most have, through their employers, traceable if indirect ties to multiple research grants, clinical research arrangements, and a vast array of paid-for health care services. As the law is now interpreted, any of these interconnections can give rise to a potential conflict—and thus require either exclusion or a waiver—for an advisory committee member.

Relatively few such interconnections, in my judgment, ought realistically to be viewed as jeopardizing the impartiality of a committee member's advice. And this, as I understand it, is the central concern of the conflict-of-interest laws, i.e., a concern to prevent governmental decision making, or in this context advice obtaining, from being compromised by the self-interest of the advice giver. The implication of this judgment is that a large, but indeterminate, percentage of the presumptive exclusions revealed by the FDA's system of comparing committee member interests (including employer interests) with committee agendas are plausible, if not compelling, candidates for the exercise of the Commissioner's waiver authority.

The goal sought by the IOM committee's recommendation is the development of general criteria or guidelines that facilitate decision making about the appropriateness of waivers in individual cases. We believe that it should be possible to identify and articulate categories of interests that ordinarily ought not be considered disqualifying, i.e., should be considered waiverable. It also may be possible to identify other categories that ordinarily should be considered disqualifying. And it may even be possible to enunciate criteria for deciding whether a committee member should be allowed to participate even with a significant potential conflict in a particular matter because of his or her importance to the committee's deliberations.

The recent history of the development, review, and approval of (b)(3) waiver requests for members of the FDA advisory committees, recounted in the IOM committee report, illustrates the consequences of the failure to develop general criteria for approving such requests. For some months now, each new waiver request appears to have been treated as a novel case,

requiring extended negotiations over the appropriateness and terms of granting a waiver and the content and format of the document explaining the agency's decision. Such a case-by-case approach virtually assures that the process will prove both burdensome and deeply frustrating.

The IOM committee found signs that officials in the FDA and OSCE recognize the need to regularize the waiver review process and reach agreement on the treatment of certain categories of potential conflicts. The committee's recommendation is essentially that this effort be extended and given priority.

The product we visualize would be a series of written guidelines, or even a grid, for decision making. For example, one "guideline" now under consideration by the FDA and OSCE would say something like: "The fact that a committee member's institutional employer operates a hospital or clinic that dispenses and charges for the FDA-regulated products, including products of the manufacturer whose application is to be reviewed, will not ordinarily be deemed disqualifying. Accordingly, a waiver to allow him or her to participate in committee deliberations is appropriate." Without necessarily endorsing this illustration, the IOM committee's hope is that other classes of interests that under the law would be presumptively disqualifying can be generically categorized as waiverable or as not waiverable.

There are many obstacles to the achievement of this goal. Some are empirical. It requires comprehensive knowledge that may not be easily assembled about the types and magnitudes of interests that the FDA committee members report that now trigger exclusions. We were given many examples, but no information that would allow a judgment about which potential conflicts were representative or how often any one occurred.

Another set of obstacles is institutional. Since many decisions about whether a type or size of interest should be viewed as disqualifying are, ultimately, matters of judgment, it is to be expected that individuals will disagree about the proper disposition of paradigm cases. The present arrangements arguably require the concurrence, or at least the acquiescence, of three offices—the FDA Commissioner, the OSCE, and the Office of Government Ethics—before any waiver can be approved. Achieving agreement at this level on any set of generic guidelines is likely to be a long-term task.

This Appendix addresses a third set of obstacles to the achievement of what the IOM committee has termed "codification." For lack of a better word, I will label these "analytical." In order to decide whether a particular kind of interest should disqualify a committee member, or, since the statute treats most interests as disqualifying, whether a waiver is appropriate for a given committee member, one needs to have some understanding of the underlying goals of the conflict-of-interest law. I suggest that the primary

goal should be to prevent the participation of committee members whose advice *might*, because of self-interest, be distorted. One could add to this formulation, as the present law does, a qualification: If a member's value to the committee's deliberations is great enough, even some risk of distortion may be accepted.

This formulation of the statutory goal is not quite congruent with the language of 208 (b)(3), which arguably calls for an individualized judgment about a member's value to committee deliberations in every case. However, because the determination of a member's value appears to be a more complex inquiry, I believe it would be more fruitful to concentrate first on the dimension that requires consideration of a waiver in the first place—the presumptively disqualifying financial interest—and see if it is not possible to categorize and then rank such interests in terms of their potential to undermine impartial advice-giving. I also believe that this is not only possible but compatible with the statute.

It seems to me quite plausible to argue, for instance, that for some sorts of interests—though perhaps not many—the threat to impartiality is so negligible that the fact of selection for committee membership should be taken as sufficient evidence of a member's value to the committee's deliberations. The willingness of the FDA and OSCE to consider agreeing that employer health care delivery activities, e.g., university hospitals, should never (or rarely) be viewed as disqualifying—i.e., should be automatically waiverable—is evidence that this legal interpretation is not preposterous.

I should add that even if it proves difficult to reach agreement on many other automatically waiverable classes of financial interests, the exercise of categorization and ranking should help improve relations between the agency and the OSCE. One frequent complaint that we heard from the FDA officials was that they never knew what the rules were. This can be translated as "we never know what sorts of interests would really raise eyebrows at OSCE." The waiver review process would be greatly improved if it were possible for the OSCE to say, and the FDA officials to know (even if they do not agree), what sorts of interests will be most difficult to grant waivers for.

On the other hand, OSCE staff members might develop a greater understanding for the agency's position if the FDA officials were able to articulate the factors that they consider important in assessing a committee member's value to committee deliberations. The attitude that committee membership—another live body eligible to vote—is all that is necessary to convince center personnel that an individual member, despite a significant potential conflict, is absolutely crucial to deliberations cannot inspire confidence that the FDA is exercising the sort of discriminating judgment that the law seems to contemplate.

The effort suggested could have value beyond assisting the FDA and the OSCE in preparing and reviewing proposed (b)(3) waivers. The part of the task discussed in this Appendix—classification of disqualifying financial interests in terms of their likely effect on committee member impartiality—would be directly relevant to the Office of Government Ethics' consideration of possible (b)(2) waiver regulations. The reader will recall that section 208(b)(2) allows the OGE—and only the OGE—to promulgate regulations categorically exempting certain types of magnitudes of financial interest as "too remote or too inconsequential' to affect a government employee's honest performance of his or her functions. This sort of waiver does not require an assessment of the employee's, e.g., the committee member's, importance to committee deliberations. Thus the effort to identify types of financial interest whose potential influence is so improbable that mere membership can be considered outweighing is a logical prelude to the exercise that the OGE must eventually undertake to implement (b)(2).

The OGE should welcome the FDA/OSCE effort, even if it does not agree with every part of their classification. The FDA/OSCE analysis should advance thinking in this most difficult area and provide examples of (b)(2)-waiverable interests that are common among medical and scientific researchers but perhaps not frequently encountered among other federal personnel.

What can be said, if anything, about the sorts of interests that ought to be considered as jeopardizing a committee member's impartiality? Although the following discussion reflects personal judgments, it may offer the beginning of a framework for thinking about that question.

For me, certain generalizations seem plausible, though not incontestable. The *magnitude* of a financial interest surely is likely to make a difference; we would worry more about a committee member's objectivity, in assessing a company's product, if he or she owned shares of stock in the company than if he or she owned one share. The law may not see a difference here, but most people do. And the law would appear to allow this difference to be accorded weight in a decision whether to grant a waiver.

Differences of magnitude—at least in ownership interests or direct payments—are relatively easy to discern and deal with. At least they are easy to array on a chart or grid. It may not be easy to agree on what threat to impartiality is presented by interests of different sizes. And searching for agreement at several different levels may not be worthwhile. Perhaps it should be enough to reach agreement on "de minimis" levels that would, if not exceeded, ordinarily allow a waiver. (We are not speaking about establishing a de minimus standard for applying the presumptive disqualification of 208(a), but rather are seeking one measure of the presumptively disqualifying interest that define its eligibility for waiver. In short, we are not

quarreling here with the prevailing interpretation of 208(a), which holds that even a single share of stock or a $100 speaking honorarium is a prohibited interest, although in another context many of us surely would do so.)

Matters get more complicated when one tries to categorize financial interests by type. But the exercise is not futile. It is possible to frame generalizations about what kinds of interests are more worrisome than others. The central question that seems likely to help clarify thinking about which interests really threaten impartiality is "whose interest is it?" This question can be examined with reference to employer interests and personal interests. The statute forbids a committee member's participation in any matter in which he or she, a family member, *or* an employer holds any financial interest. I suggest that personal (including family) interests are more likely to threaten an individual's objectivity than the financial interests of his or her employer. To be sure, one can think of examples of both sorts that would defy this generalization, and perhaps—on close examination—those examples would swallow the principle. Even so, as one starting place for analysis, it is likely to prove helpful to make the personal-employer dichotomy one of the dimensions of a grid of financial interests, all of which under the current law are deemed presumptively disqualifying.

We have been provided examples of three types of employers' interests that are believed to trigger section 208(a): (1) sales by the employer, or by a subordinate unit of the employer, of the FDA-regulated products made by companies that have new product applications pending before the FDA; (2) research or other grants from such companies; and (3) gifts from such companies to support institutional programs, e.g., an endowed chair. No doubt there are other many others, among which it ought to be possible to draw distinctions based on the likelihood that a committee member might modify his or her advice in order to protect an employer's relationship with a company. It would not be imprudent, in my view, for the FDA to take the position that interests falling in the first category ought always to be waiverable absent clear evidence that the employer receives a substantial amount of its income from such sales or that the committee member him-or herself benefitted personally from decisions affecting the usage or sale of the company's product. A similar judgment might be supportable for research grants other than those made to a committee member personally.

My goal here, however, is not to offer conclusions about which kinds of employer interests ought to be considered routine, possible, or unlikely candidates for waiver, but simply to suggest an approach to thinking about this question. The approach involves, first, the categorization of the various types of employer interests the FDA committee members have displayed and, second, thoughtful assessment of the likelihood that interests within a

particular category will undermine an individual committee member's impartiality.

The same sort of exercise is appropriate in assessing the personal interests of committee members. To simplify the task, it might well be prudent to conflate member interests and family interests, i.e., to assume that a spouse's or minor child's financial interest is as likely (or unlikely) to affect a member's impartiality as his or her own. It would be a crude generalization, to be sure, but crude generalizations will be necessary to develop a framework that can guide—and, which is the ultimate goal, simplify and thus expedite—review of individual waiver requests.

Within the category of personal interests, individual research grants are apparently a common source of presumptive disqualification. The dollar value of a grant probably ought to be a consideration in assessing the likelihood that it may affect a committee member's impartiality. But equally important, it seems to me, is the extent to which a grant contributes to a researcher's personal income, as distinct from institutional income. I would be inclined, as well, to differentiate between research grants provided in the past and grants that currently support a member's research. The influence, if any, of the former must be in the member's hope for future research support from the same source, and I do not find it implausible that an individual's judgment is less likely to be influenced by a hope that support might someday be renewed than by the fear that current support may be terminated.

I would, at least tentatively, draw a similar distinction between other sorts of company payments to a committee member. A concluded consulting arrangement that once paid a $2,500 yearly honorarium strikes me as less worrisome that an on-going relationship that provides rewards, even of smaller magnitude, in future years.

Indeed, it may be appropriate to draw a broader distinction between interests that a member already owns, and whose value will not significantly change, and interests whose enjoyment, or whose value, may depend on the success of the company that is the source of the interest. A consulting fee paid in the past may be the source of hope for future beneficial relationships, but its value will not be diminished if the company never provides support again. By contrast, the value of stock owned by a committee member in a company whose products he or she is asked to evaluate is clearly affected by the future success of the firm, and very possibly by the profitability of the new product.

The range of personal financial interests that one can assemble from examples provided by the FDA is large, and their variety may appear to defy any systematic effort at description, much less a categorical assessment of their likely affect on impartiality. But one cannot know this without making

the effort. And there is a value to the intellectual exercise even if a formal decision making grid or set of decisional guidelines remains incomplete. It will force those involved to articulate and explain their judgments about the appropriateness of granting waivers in specific cases. It may also yield—and this would be no small achievement—a common vocabulary for describing and analyzing individual cases. And, if engaged in jointly by officials from both the FDA and the OSCE, it may help to reveal common ground and to clarify differences.

The discussion thus far has focused on only the first element of the statutory formula for granting (b)(3) waivers—the potential of different types and magnitudes of financial interests to undermine a committee member's impartiality. Section 208(b)(3) also requires consideration of a member's importance to committee deliberations. The suggestion made here is that some interests can be classified as so unlikely to threaten impartiality that selection for committee membership can be taken as sufficient evidence of importance to offset the remote risk. But there may be few such interests, and they are likely to be an employer's rather than personal or family interests. Thus, in evaluating many waivers attention must be given to a member's importance to committee deliberations. I believe that this second element should also be susceptible to categorical analysis, i.e., it should be possible to formulate guidelines for evaluating individual cases. And the committee's recommends that this should be done.

There is one additional point to be made. Many readers may ask how the exercise sketched in the foregoing paragraphs fits with the statutory regime for regulating financial conflict of interest. The answer has already been suggested but warrants reiteration. Section 208(a) of the conflict-of-interest statute sweeps very broadly and, I acknowledge, as construed makes the sorts of distinctions discussed above irrelevant to a determination of whether an interest presumptively disqualifies a committee member from participating in advice on a particular matter. But section 208(b)(3) calls for an assessment, by the Commissioner of Food and Drugs, of the likelihood that a disqualifying interest will in fact affect the member's objectivity, as when as of his/her importance to the committee's deliberations. Such an assessment logically invites, and surely permits, consideration of the sorts of distinctions I have suggested.

7

Committee Operations

The conduct of an advisory committee meeting involves many elements. This chapter considers the following: setting the advisory committee agenda, scheduling committee meetings, meeting preparation, the conduct of a meeting, and meeting follow-up.

Although some explicit policies guide FDA advisory committee operations, relatively few current policies are documented. One question that confronted the IOM committee, therefore, was to determine how much written policy guidance was needed to ensure effective performance. Although such guidance provides the basis for uniform practices, it may also introduce unnecessary and unwanted inflexibilities.

Just as there are differences among FDA's centers in the recruitment of members and the assignment of functions to committees, committee operations currently reveal substantial variation among and often within centers. This variation originates from differences in their statutory missions, histories, administrative cultures, the scientific and clinical field in question, and the personal habits of the relevant FDA officials.

Some variation among and within centers is justified, and the IOM committee wishes to avoid recommending inappropriate standardization in such cases. In general, however, substantial standardization of policies and procedures in advisory committee operations is both desirable and feasible, the benefits of which will accrue to the agency, the sponsors, and the general public.

The IOM committee recommends that the FDA develop uniform management guidelines for advisory committees applicable across all three centers and that it eliminate unnecessary differences in the management of committees.

SCHEDULING ADVISORY COMMITTEE MEETINGS

The IOM committee deliberated at length about recommending that FDA adopt a policy of scheduling advisory committee meetings as long as one or even two years in advance. Meetings scheduled in this way would require the following associated deadlines: agency (and presumably sponsor) agreement to review an application at a scheduled meeting; timely sponsor submission of all data to go to the advisory committee; timely completion by the agency of its review; and on-schedule distribution of material to the advisory committee members.

The proffered referent in this case is the submission of a research grant proposal to the National Institutes of Health (NIH) by a specified date to ensure its review at a particular time. Included in this scheme is a decision rule that late applications are not reviewed until the next cycle. Although the committee recognizes that the NIH experience provides an imperfect comparison for the submission and evaluation of an application to the FDA, it believes that there is great merit in introducing some comparable discipline in the FDA review process.

At least three reservations about such a proposal have been expressed. First, scheduling conflicts with major professional society meetings could occur. This is the least serious problem and could be handled similarly to NIH procedures. (NIH schedules grant proposal cycles and study section meetings one or two years in advance and consults with the major professional societies in particular fields before doing so.)

Second, in informal discussions industry representatives responded favorably to advance scheduling provided the particular advisory committee met at least three times per year and on a regular basis. The "cost" of three or four months delay if a meeting deadline were missed under such circumstances was seen as tolerable. Indeed, working to deadlines elicited a generally favorable industry response. However, for those advisory committees that met only twice a year, failure to meet the associated deadlines would result in a slippage of six months; the industry representatives did not find this period acceptable.

The most serious reservation was voiced by FDA representatives, who expressed the view that establishing a certain date some 6 to 12 months in advance for the end of an FDA review would be very difficult. Furthermore, meeting such advance deadlines would impose a demand on scarce agency resources of medical reviewers, which would make it difficult for the agency to comply easily.

The IOM committee saw the benefits of advance scheduling as twofold: imposing greater discipline on the internal product evaluation process, and making it easier to schedule the time, and thus ensure the participation, of

busy advisory committee members. Currently, the scheduling of advisory committee meetings is affected by the availability of committee members, the length of FDA review times, deference to a sponsor's desire to submit data up to the last minute, and long-standing agency practice of scheduling meetings on an ad hoc basis.

Modification of current practice would require that the agency issue an explicit policy on advance scheduling, plan for an appropriate transition period, and carefully monitor the implementation of scheduling in the transition period. The IOM committee believes that advance scheduling would be justified as a means for making better use of advisory committees.

The IOM committee recommends that FDA adopt a policy of annual advance scheduling of advisory committee meetings and of meeting agendas, with review cycles having deadlines for sponsor submission of data, FDA completion of reviews, and advance distribution of materials to committee members.

MEETING PREPARATION

General Criteria for Setting the Agenda

The criteria for determining the matters to be brought to an advisory committee vary from center to center. CDRH, for example, was obligated by law to bring *all* PMAs to an advisory committee until the Safe Medical Devices Act of 1990 gave it some limited discretion. CBER brings both product-related biologics development and intramural research issues to its advisory committees.

Only one center has a written policy. CDER recently clarified its general criteria in a September 1991 document,[1] that identified a range of matters that the agency might bring to an advisory committee. These include advice on the approvability of specific drugs, general drug development issues, issues pertaining to marketed drugs, and management of the new drug evaluation (NDE) program. We examine the components of this document below.

Product Evaluation and Guidelines Development at CDER

The first of these matters, advice on the approvability of specific drugs, usually pertains to a new chemical entity (NCE) but may also include a new indication for a marketed drug. Advice may be sought on the following aspects of a given application: adequacy of the clinical trial design and the conduct of studies to provide substantial evidence of effectiveness; adequacy

of the data supporting safety; adequacy of the data about dosing and scheduling; consideration of surrogate endpoints, as appropriate to the compound; the need for postmarketing surveillance or additional studies; the need for limiting indications to specific populations; the overall risk-benefit of a new agent; special labeling concerns; and switches of prescription drugs to over-the-counter (OTC) status. On occasion, the center may ask an advisory committee member to conduct a primary review of selected portions of a new drug application (NDA).

Issues of drug development that go beyond the evaluation of specific products on which advice may be sought include development guidelines for classes of drugs, discussion of clinical study design issues, and specific safety issues for particular drugs. The Cardio-Renal Drugs Advisory Committee, for example, held a two-day advisory committee meeting this past year, the first of which dealt with the question of dose-response measurement of angiotensin-converting enzyme inhibitors. In addition, the center may seek advisory committee counsel on marketed drugs when adverse drug reaction data emerge from surveillance, animal studies, or new clinical trials.

Program Management at CDER

Product evaluation issues, broadly construed, receive the greatest attention in the CDER document on advisory committee agenda items. However, the document also suggests several subjects for advisory committee agendas that relate to the management of the NDE program. The first deals with the periodic review (usually annually) by an advisory committee of the pending NDAs and the major new indications of other drugs in the CDER pipeline. The center's emphasis is on those drugs that may have an important public health impact, whose development is unusually complex, or that are subject to great public scrutiny.

Second, the periodic review of "important products under development" involves using committees earlier in the product development process than the licensing stage. The Lasagna Committee report called for this kind of early involvement, especially for cancer and AIDS drugs. The FDA argues—correctly, in the judgment of the IOM committee—that defining early involvement as participation in the review of investigational new drugs (INDs) is a practical impossibility. The inventory of active INDs is quite large, a substantial number of new INDs are received each year, and the agency is required by law to assess the safety of a planned clinical study within 30 days of the IND's receipt (lack of response by the agency allows the sponsor to initiate the clinical trial). Thus, it is not feasible to routinely involve advisory committees in initial IND reviews.

Nevertheless, the impact of AIDS on drug development and evaluation has been to involve CDER more deeply in clinical trial protocols than has been true historically. A similar early involvement is taking place in oncological drug development.

The CDER statement explicitly contemplates that reviewing divisions will periodically review the IND "portfolio" with their advisory committees. The presumed benefits of such a review are guidance to the agency and a clearer sense of participation by advisory committee members. The factors limiting the pursuit of this policy include the resource costs to agency personnel and to advisory committee members, as well as the disclosure of early-stage proprietary information to an increased number of individuals.*

The third innovation suggested in the document is the most far-reaching. It is that advisory committees consider the periodic analysis of priorities and resource allocation for management of IND applications, NDAs, abbreviated new drug applications (ANDAs), and NDA supplements.

The IOM committee commends CDER for this clarifying document and recommends that CBER and CDRH develop similar statements. The IOM committee also recommends that each center schedule an annual review by each advisory committee of the major NDAs and INDs (or their equivalents) that are anticipated to come before their respective reviewing divisions.

Setting the Agenda

Setting the agenda of an advisory committee meeting involves two stages: (1) formally scheduling a meeting and publishing an announcement of that meeting in the *Federal Register*, and (2) a few days before the meeting, sending committee members a detailed agenda with specific questions on which advice is sought.

The first stage of this process is initiated by the *Federal Register* announcement, which must be published at least 15 days before a meeting is held. Publication lead time requires that an announcement be submitted by the center about six weeks before a meeting. The announcement sometimes includes a general description of the agenda, for example, the

* Traditional vaccine development has involved CBER with vaccine sponsors from the inception of a product through its clinical trials to the product licensing stage. This reflects both the public health nature of vaccine development as well as a relatively modest CBER workload. The impact of the biotechnology revolution, however, is beginning to increase the CBER workload and may force the center toward less involvement in early stage reviews.

specific NDA of a given sponsor (identified by number) and the general topics of the meeting.*

The IOM committee recommends that *Federal Register* announcements of scheduled advisory committee meetings routinely include the most detailed statement of the agenda that is feasible with existing time constraints.

Members of the IOM committee who serve on FDA advisory committees noted that they seldom see the *Federal Register* announcement.

The IOM committee recommends that the *Federal Register* announcement be sent routinely to advisory committee members when it is submitted for publication.

The general questions that the FDA must consider in assessing the safety of drugs and biologics are whether the risks of a compound are outweighed by its benefits and whether there is "substantial evidence" from well-controlled trials to support the claims of effectiveness. It would help the review process if advisory committee members were regularly reminded of these decision criteria as they review a sponsor's data.

The IOM committee recommends that the FDA routinely send the general statement of the regulatory criteria governing product evaluation to each advisory committee member in advance of a meeting to assist members in framing their review of the data.

The second stage-setting the detailed agenda of committee meetings—involves establishing the specific meeting topics and time allocations and preparing the specific questions that the advisory committee will consider. Of these steps, preparing the questions is the most important.

The FDA is primarily responsible for determining these questions. It has the statutory responsibility to review and approve applications, and convenes committees to assist it in that process. As a practical matter, this is the only feasible way to proceed. The division director, in consultation with the office director, usually develops the specific questions. FDA preparation, review,

* The Generic Drugs Advisory Committee meeting of September 26–27,1991, example, was to consider the "assessment of pharmacokinetics topics (rate and extent of absorption) in the determination of bioequivalence" and "statistical topics (data transformation, sequence effect, and outlier analysis) in the determination of bioequivalence" on successive days.

and approval of questions may take several weeks; they are often sent to committee members just a few days before a meeting.

Three issues have been raised about this process. First, some observers believe that the advisory committee should set its own agenda. (The Lasagna Committee comes close to recommending this.) If advisory committees were adjudicatory bodies responsible for weighing both the sponsor's data and analysis and the FDA's critique, and then rendering a judgment, an argument could be made that they should have control over their own agendas. Because the committees are *advisory* to the FDA, however, and are convened to assist it in the administrative review of drugs, biologics, and medical devices, it is logical to argue that the agency should develop the committee agenda around the matters on which it wishes advice.

The other two issues are of greater concern to the IOM committee. A recurring criticism of FDA's behavior toward advisory committees is that agency officials—typically the reviewing division—seek to control or influence, or even manipulate, a committee to achieve an outcome that they desire. This charge of "undue influence" is often made about the teleology of the questions posed to a committee; that is, they appear to some observers to be phrased or ordered so as to lead the committee to a conclusion that reflects the preference of the division in the matter. The other complaint, which is closely related, is that advisory committee members seldom have an opportunity to modify the questions prepared by the agency or to add others that they wish to consider.

These issues can be addressed together. It is seldom feasible to involve the committee deeply in advance consultation on questions because of time constraints and the lack of familiarity of members with the specific issues presented by an application. Two actions are possible, however, both of which would improve the process and mitigate the charge of undue influence. First, the questions, which are often developed solely by FDA staff, could be prepared in consultation with the committee chair. Second, the agency could and should inform committee members that they have a right to modify agency questions or add questions of their own.

The IOM committee recommends that in the formulation of meeting agendas and of questions, the advisory committee chair be routinely consulted as a standard procedure. It further recommends that committee members be routinely informed that they may modify FDA-prepared questions, based on their review of the data, and introduce questions of their own before or at an advisory committee meeting.

Content of the Agenda Questions

One issue raised by the Industry Liaison Panel is whether FDA questions should be restricted to an application's scientific and clinical matters or whether they should also extend to the regulatory questions that the FDA must face. The panel's report stated the following: "In cases where a drug or biologic marketing application is under consideration by a committee, the FDA should not ask the committee to advise it on whether or not the application should be approved but, rather, on whether substantial evidence of safety and effectiveness has been provided." The panel recognized that this question was usually but not always asked of drugs and biologics committees, and recommended its uniform use. It also acknowledged that the CDRH interprets its statutory authority as requiring that the advisory panel be specifically asked whether an application should be approved.

The agency decision to approve a drug or biologic is based on two criteria: whether there is "substantial evidence" (consisting of adequate and well-controlled trials) to support the claims of effectiveness; and whether the risks of a product have been shown to be outweighed by its benefits. Given these criteria, Dr. Robert Temple, Director of the CDER's Office of Drug Evaluation I, commented on the panel's point about the distinction between the scientific and regulatory questions. "Once a committee has said there is substantial evidence of effectiveness derived from adequate and well-controlled studies and that the benefits outweigh the risks," he wrote, "it is being unduly coy to suggest that we should not ask whether the committee recommends approval."[2] The IOM committee concurs with Temple regarding the "distinction without a difference."

The IOM committee believes that FDA reviewing units should be free to ask advice on both scientific questions and related regulatory implications, as they deem important.

A related issue is the charge that the FDA sometimes asks "loaded" or leading questions. It is necessary to distinguish here between the tone and objectivity of questions and the fact that the asking of particular questions will indicate the problems that the FDA has with an application.

The IOM committee recommends that questions asked of advisory committees be fair and objective in tone and avoid language that might be considered biased or inflammatory. However, the committee is not troubled that precise questions often will reveal the agency's concerns about an application.

Timely Distribution of Materials

A major recurrent complaint from advisory committee members is that the FDA often fails to distribute materials sufficiently in advance of a committee meeting to permit their careful review by members. Delays in the distribution of materials are attributed primarily to limited personnel and administrative resources, the natural tendency of reviews to get done at the last minute, and the tolerance of such practices by the agency. A more sinister charge is that such delays are part of a deliberate effort by agency officials to manipulate the work of advisory committees.

There is a virtual consensus that the effective use of advisory committee members requires that they have review materials in their possession for a reasonable period of time before a meeting, preferably, for at least three weeks.

The IOM committee recommends that the agency adopt and follow a strict schedule for advance distribution of materials. The meeting agenda, sponsor's data and analyses, and agency reviews should be delivered to members at least three weeks in advance of a meeting. The specific questions for the meeting should be delivered no later than 10 days before a meeting.

The IOM committee believes that the responsibility for fulfilling this recommendation rests not only with committee executive secretaries, but also with the directors and the application reviewers of the appropriate division. It also believes that advance scheduling of committee meetings should facilitate compliance with this recommendation.

Summaries of Materials Sent to the Committee

Advisory committee members complain that often the format of materials they receive from a sponsor is not conducive to a careful review of the data. Sometimes this complaint is accompanied by a request that the FDA "repackage" sponsor materials to facilitate review. The agency does not wish to be responsible for the presentation of a sponsor's work, since this could be cited as a means of influencing a committee's analysis. A major deficiency could be remedied, however, through the use of concise (20–25 pages), complete, and integrated summaries of the sponsor's application and the agency's review.

The IOM committee recommends that the FDA develop a standard format for sponsors to summarize their application briefly yet compre

hensively, as well as a comparable format for a summary of the agency's review. These summaries should be provided in addition to the materials normally sent to advisory committee members.

Use of Primary Reviewers

The CDRH assigns primary review responsibility for a particular PMA to one advisory committee member, mainly to obtain a clinical evaluation of the application. The IOM committee believes that this practice also ensures a more thoughtful committee discussion and distributes the work load within the committee. In addition, this practice has great utility in those situations in which the match between committee expertise and a particular agenda item may be weak. (See the "custom tailoring" discussion below.)

The IOM committee recommends that the three centers consider the routine assignment of one member of the advisory committee to conduct the principal review of each application.

Communications Issues Before an Advisory Committee Meeting

Five types of communication before an advisory committee meeting deserve attention: FDA communication to committee members; communication among members; communication between sponsors and members; FDA communication to sponsors; and FDA communication to the public.

FDA Communication to Advisory Committee Members

Advance communication by FDA officials with advisory committee members before a meeting has generally been limited to one member at a time. The impression gained by the IOM committee during its study, based on discussions with FDA staff, was that agency personnel believed that they could not discuss any substantive issue with more than a single advisory committee member at a time without violating the Federal Advisory Committee Act (FACA). This impression was reinforced by the IOM committee members who were or had been FDA advisory committee members.

However, when asked by the IOM committee about the ground rules for communications from FDA personnel to committee members, the Chief Counsel to the FDA responded in this way:

> In our view, FDA staff could legally discuss such *preliminary* issues as agenda topics, materials, and questions with a part of an advisory

committee that was less than the full committee without the individuals having the conversation being "utilized" as an advisory committee and without having the conversation deemed a meeting. Indeed, the *National Anti-Hunger Coalition* case suggests that a combination of agency staff and committee members may even hold substantive discussions outside of announced committee meetings, if the discussions are preliminary, are of a staff nature, and do not involve giving advice to an agency, and so long as any preliminary advice arrived at is rendered to the agency by the full committee.[3]

The practices of some FDA centers, she suggested, may be stricter than necessary to reduce any legal risk.

One caveat suggested by the Chief Counsel was that the Office of Government Ethics (OGE) may hold the opinion that review of materials by an advisory committee member before a committee meeting may constitute participation in "a particular matter" and thus require screening for conflict of interest and, if necessary, the issuance of a waiver before it takes place. "This is not," she wrote, "current practice at FDA." The extension of the OGE view to FDA communication with some committee members might require conflict screening and the issuance of a waiver, even for discussions that are preliminary. Several attorneys who communicated with the IOM study contended that any agency communications with advisory committee members before a meeting should be regarded as ex parte communications and that procedural guidelines should be established to restrict them. The law does not treat agency communications as ex parte; thus, procedural guidelines of the kind envisioned are not required. The need for such guidelines turns on the conceptualization of advisory committees: whether they are adjudicatory bodies hearing the presentations of two contending parties or advisory adjuncts to the administrative process. If the former, detailed guidelines for communication between agency and advisory committee members before a meeting may be appropriate. If the latter, the need for such guidelines becomes less compelling. The IOM committee strongly believes that the latter definition applies to the advisory committees used by the FDA. Thus, the current level of concern about interactions between FDA staff and advisory committee members may be misplaced.

The IOM committee notes this discrepancy between what guides agency practice and the views of the Chief Counsel, endorses the opinion of the latter, and recommends that the FDA clarify its guidance to FDA staff and to advisory committee members.

Communication Among Advisory Committee Members

The FACA has also been interpreted by some FDA officials, and in consequence by many advisory committee members, as precluding telephone or face-to-face communication between two or more committee members in the period after receipt of the materials to be reviewed at a forthcoming meeting but before the meeting itself. This presumed limitation has been interpreted to prohibit, for example, consultation by a clinician committee member with a statistician member on matters of clinical trial design, data analysis, or data interpretation. The rationale for such a prohibition stems from a desire to preclude a minority of any advisory committee from establishing a position before a meeting and exerting influence favoring that position in committee discussions.

The presumed limitation unnecessarily restricts discussion among committee members and is not required by the FACA.* Again, the FDA Chief Counsel has written that "that preliminary discussions among committee members do not violate FACA." In short, staff instructions against such consultations may seem overly cautious.

The IOM committee notes a discrepancy between practice in some parts of the agency and the views of the Chief Counsel, endorses the opinion of the latter, and recommends that the agency clarify the legal bases governing communication among advisory committee members. If, as expected, the Chief Counsel's opinion reflects agency policy, this should be clearly communicated in writing to all FDA personnel who deal with advisory committees, to committee members themselves, and to other interested parties. Preliminary discussions among members to clarify technical issues for information purposes only should not be discouraged; the limits on such consultations should be clearly defined; committee members should be instructed to document such consultations by a log or other, similar means; and these consultations should be disclosed at each committee meeting.

The issue of FDA communication to advisory committee members and communication among members is poorly understood both within FDA and outside the agency. It is very important that the agency clarify the legal issues governing such communication and provide appropriate written

* When this limitation is coupled with committee meetings that are almost entirely public, it greatly attentuates the benefit of the intellectual give-and-take among experts that provides the initial impulse for convening advisory committees.

guidance to FDA staff, all advisory committee members, and other interested parties.

Communication Between Sponsors and Advisory Committee Members

As a matter of FDA policy, sponsors are discouraged from communicating directly or indirectly—save through the agency—with advisory committee members before a meeting. The agency informs sponsors and committee members of this stricture. This policy is designed, in general, to protect the independence of the committee from lobbying by sponsors.

The IOM committee affirms the soundness of this policy.

Agency Communication to Sponsors

The FDA is governed by the Freedom of Information Act, (21 CFR 20), and federal confidentiality laws with regard to the public disclosure of materials it provides to advisory committee members. The agency is not obligated to share with sponsors, or the general public, all of the information provided to advisory committees. "Draft questions, proposed agendas, and FDA staff analyses" are exempt from the public disclosure requirements of 5 USC 552(b)(5).

The FDA takes the view that it is not obligated to share with sponsors its communications to advisory committee members in advance of a meeting. The IOM committee believes, however, that it is appropriate for the FDA to provide sponsors with copies of all information that it sends to advisory committees. This facilitates the preparation by the sponsor of its response to agency questions.

The IOM committee recommends that the FDA provide sponsors of applications with the same materials that it sends to advisory committees. Questions should be sent to committees and sponsors on the same schedule.

Communication Between the FDA and the Public

Regarding the public release of the questions prepared for the advisory committee, the general practice of the FDA has been to make them available to the public on the morning of a meeting. The IOM committee agrees with this practice and does not recommend earlier release to the public. The report by Kutak, Rock & Campbell, which dealt with FDA's handling of financially sensitive information, basically concurred that FDA release of the

questions to the public on the morning of a committee meeting was sound practice.[4]

The IOM committee did not examine at any length the questions regarding FDA advisory committees and the effect of their management, including the time of the public release of the questions prepared for committees, on trading in the securities markets. The FDA has before it the Kutak Rock report on financially sensitive information and this IOM report on advisory committees and must address the implications of where these two reports intersect and make the appropriate policy determination.

CONDUCTING AN ADVISORY COMMITTEE MEETING

The primary objective of an advisory committee meeting should be to facilitate the independent, thorough deliberations of committee members. In this context, independence means freedom from influence by the sponsor of the product under consideration, by any other interested parties, and by the agency itself. To provide this independence, a secondary objective should be to minimize the opportunities for the FDA, or other parties, to exert undue influence, or to appear to do so, over committee deliberations. The discussion and recommendations of this section are directed toward achieving these objectives.

Roles of the Principal Participants

There are invariably four principal participants in the typical advisory committee meeting: the committee members, the chair, the FDA professional staff, and the sponsor of an application. Consultants also function in significant ways in many committee deliberations.

The role of advisory committee members is to provide independent, expert scientific advice to the agency by responding to specific questions about study design or methodology, adequacy of data, and assessment and interpretation of risks and effectiveness that have been identified by the FDA professional staff. The ability of committee members to carry out such a role is facilitated by their expertise, the provisions for advance preparation discussed above, and the "rules of the game" for committee meetings, which are discussed here.

The role of the advisory committee chair is critical to the effective performance of a committee. The chair should control agenda time efficiently; protect committee discussion time; ensure, in consultation with agency staff, that the meeting arrangements facilitate committee deliberations; regulate, as necessary, media coverage of meetings; and ensure that

committee deliberations are brought to closure by providing clear advice to the agency on the questions asked of the committee.

FDA staff are involved in the substantive evaluation of an application and in the organization of an advisory committee. Those who review an application have the responsibility to evaluate the completeness, adequacy, and relevance of the data; the analyses of and conclusions drawn from the data; and the completeness of the information presented in the request for approval. When necessary, FDA staff may arrange for a consultant to carry out further analyses of the data or assessments of their sufficiency.

In CDER and CBER, the executive secretaries are primarily responsible for the organization and logistics of the advisory committee meeting. In CDRH, they play a somewhat different role that derives from their dual responsibilities as managers of the substantive review and as administrative support to the committee. In their former capacity, they participate in the deliberations in a manner similar to division directors in CDER and CBER; in their latter capacity, they perform similarly to the executive secretaries in the other two centers.

Product sponsors are the final significant group that participates in an advisory committee meeting. The sponsors usually make a presentation of the data on their product in preparation for an argument that the product should be approved. The sponsors may use consultants to present these data, as well as individual patients or practitioners to testify on their behalf.

Allocation and Control of Agenda Time

Two phenomena are regularly mentioned by advisory committee members as impeding committee deliberations. One is that sponsors' presentations often absorb more time than is initially allocated by the agenda. The possible reasons for this are several: the initial time allocation may not be realistic, which calls for prior consultation between agency staff and the chair; the members may wish to question the sponsor at greater length than anticipated, which suggests the need to poll members in advance for their questions so that the concerns of several members can be aggregated; or the sponsor may consciously present more data than the allocated time allows, which calls for a prior commitment from meeting participants to adhere to the schedule. Similarly, FDA staff presentations may exceed allocated time and thus impede committee deliberations as well.

The IOM committee recommends that the FDA routinely consult committee chairs in the allocation of time to agenda items and that this allocation try to anticipate points throughout the meeting at which committee questioning will be likely It further recommends that

committee chairs be instructed that the control of agenda time is one of their primary responsibilities,[*] and that they must work to protect committee discussion time, including exercising strict control on the presentations of sponsors and the FDA before the committee and attendant questions and discussions by committee members.

The principal reason for exercising strict control over the agenda is to protect committee discussion time, which is vulnerable to erosion by the factors listed above. In addition, because committee discussion is often scheduled at the end of a meeting it may lack the participation of all members, especially those from the West Coast, who begin leaving for the airport in the late afternoon.

Electronic Coverage of Meetings

Television news networks, with cameras, kleig lights, and associated equipment, are a common and often intrusive presence at FDA advisory committee meetings. Guidelines governing "electronic recording equipment," [**] but pertaining mainly to television, have been set forth in (21 CFR 10, Subpart C (200–206)). These regulations vest authority for their administration in the "designated presiding officer," presumably the chair of an advisory committee.

The IOM committee recommends that advisory committee chairs be routinely oriented to their authorities and responsibilities in regard to the control of electronic coverage of advisory committee meetings, for the purpose of facilitating committee deliberations without compromising the public's right to know.

In addition to television, the audience of an advisory committee meeting often includes individuals with other electronic devices, such as recording machines, telephones, and cameras. These are often referred to as nuisance items but pose relatively few problems for advisory committees, which conduct practically all of their business in open sessions.

[*] FDA regulations grant authority to advisory committee chair to "conduct hearings and meetings, including the authority to adjourn a hearing or meeting if the chairman determines that adjournment is in the public interest, to discontinue discussion of a matter, to conclude the open portion of a meeting, or to take any other action to further a fair and expeditious hearing or meeting" [21 CFR 14.30(a)].

[**] The term is defined as "any visual or audio recording made by videotape recording equipment or moving film camera, and/or other electronic recording equipment."

Voting

Variations exist in the use of voting by FDA advisory committees. In CDRH, all committees are asked to vote on the regulatory issue of whether a given medical device should be approved. This practice is based on CDRH's interpretation that a vote is required by the provision of the Medical Device Amendments of 1976 that calls for an advisory panel to submit a "report and recommendation ... with respect to an application" [Food, Drug, and Cosmetic Act, §515(g)(2)(B)]. CDRH advisory panels are not, however, asked to vote on the scientific questions of whether information in an application shows a "reasonable assurance" that a device is safe and effective "under the conditions of use prescribed, recommended, or suggested in the proposed labelling thereof" [Food, Drug, and Cosmetic Act, §515(d)(2)(A,B].

In CDER and CBER, voting practices follow the discretion of the committee chair or the tradition of the reviewing division. Some division directors take no votes, some ask for votes only on scientific questions, and others request votes on regulatory questions.

The IOM committee recommends that FDA adopt a policy, consistent across all advisory committees, by which committees are asked for a vote on important questions before the committee. To the extent feasible, the chair should identify in advance the issues on which votes are to be taken.

The IOM committee discussed at length a proposal by one member[5] that advisory committee votes on questions before them be scaled (for example, from one to nine), rather than binary (yes, no). This proposal is based on three premises. First, safety, effectiveness, and other factors considered in advisory committee recommendations are continuous variables. Second, given that there are no definitive empirical bases for deciding issues before an advisory committee, the FDA should seek to determine both the range and strength of the experts' opinions. Third, a good deal could be learned by frequent scaled votes about the multiple facets of component questions that come before a committee, including the distribution of views among members on particular issues, as well as any persistent voting patterns or apparent biases.

The elements of the proposal are based on the modified Delphi system used by the RAND Corporation's appropriateness-of-care studies. In the RAND approach to voting, all votes are scaled from one to nine; individual votes are secret, but each member receives the distribution and his or her vote after each round; there are usually two rounds of votes per question,

with committee discussion between each round; summary statistics are generated on each question (e.g., the median after omitting outliers); and the vote distribution and summary statistics, but not individual votes, become a matter of record.

The IOM committee was intrigued by the proposal but found it too novel and formalistic to recommend for general adoption by the FDA. The committee favored binary votes that forced individual members to resolve uncertainty in an up-or-down manner and provide unambiguous advice to the agency. It thought that scaled votes on regulatory decisions to approve or disapprove a product might be confusing to the agency and to interested parties, at least initially. However, the IOM committee commended the proposal to use nonbinary, sophisticated voting procedures and tallying to the FDA for consideration on a pilot or demonstration basis.

Agency Neutrality

Several issues were considered that relate to the neutrality of the agency in its relations with advisory committees. These include agency presentations, agency-committee interactions, and seating arrangements.

Agency Presentations

The Industry Liaison Panel emphasized the importance it attaches to neutrality of presentation by the agency. Such neutrality includes both the adoption of a dispassionate tone and the withholding of any judgment about a submission, even if asked.

Agency responses to the implications of this view vary. Some FDA officials counter that sponsor presentations routinely lack neutrality and reflect (charitably) a "best foot forward" posture that minimizes the problems and highlights the promises of an application. Those holding this view see themselves as obligated under the statutes governing FDA to act to protect the public health and to expose the weaknesses of a sponsor's submission and presentation. Neutrality, under the circumstances, is neither possible nor desirable.

Other FDA officials view the agency's responsibility as one of presenting a thorough, fair critique in a scientifically objective way and withholding any expression of a judgment about what should be done with the application. If asked for a judgment, some officials feel obliged to respond, while others decline to do so.

The response of Dr. Robert Temple to the Industry Liaison Panel report deserves quotation:

> While it is critical to be certain the committee is independent in answering our questions, it is not necessary to pretend that FDA has no viewpoint. While FDA may have reached conclusions in some cases, it may still have other critical questions for the committee. For example, we do not necessarily need to ask an advisory committee whether studies are adequate and well-controlled. We have usually given studies far greater scrutiny than the committees can and may have reached the conclusion that they [the studies] indeed are well-controlled. On the other hand, having concluded that studies are well-controlled is not the same as saying that the effect shown is of value or that the adverse reactions elicited are acceptable in view of the risks. We thus might well go to a committee believing that the studies themselves are well-designed and acceptable but asking the committee about the persuasive-ness of the outcome. In that case there is no reason to pretend that FDA has no view as to the adequacy of the studies. In other cases, we might believe that studies were fatally flawed, e.g., not long enough. We would need to know the committee's views on this, which is obviously a matter of judgment. Our questions for the committee need to pose the question clearly, so the committee can provide a clear viewpoint, agreeing or disagreeing. It is not leading the committee merely to tell the committee where FDA stands. Knowing FDA's initial view does not prevent the committee from reaching a different conclusion and FDA is prepared to revise even conclusions it thought it had reached.
>
> I thus strongly disagree with the [panel's] recommendation that questions posed to the committee should be neutral in all cases. It is reasonable to take a question to the committee that indicates a point of view by the agency so long as it is also entirely clear that the committee is invited to express a different view if that is what it believes and to explain its reasoning to the agency.[6]

The IOM committee believes that agency presentations of its reviews of a sponsor's application should reflect a critical but fair evaluation of the data. If the agency has problems with the application, the identification of which reveals the agency's conclusion (tentative or fixed), the committee sees no reason to object to the communication of those concerns. Indeed, failure to do so might be construed as manipulation by not apprising the committee of factors that will be important in the agency's official decision.

On the other hand, the IOM committee strongly believes that agency presentations about a sponsor's application should be professional in tone, and thorough, fair, and scientifically objective in their critiques. The agency should acknowledge its public health responsibilities to ensure that sponsors provide evidence of product safety and effectiveness.

FDA-Committee Interaction

One question that has been raised is how FDA staff should interact with advisory committees in the conduct of a meeting. As a general proposition, agency staff should not attempt to dominate committee discussions but should seek (with the help and under the control of the chair) to elicit the views of advisory committee members. The chair of a committee should be instructed about the importance of appropriate use of discussion time by FDA staff and should exercise control over the meeting accordingly.

Seating Arrangements

Complaints have been made that some seating arrangements at advisory committee meetings suggest an effort to influence the outcome of the deliberations. The IOM committee believes that the general principle that should govern seating arrangements is that they should be made, to the extent physical facilities permit, to facilitate the deliberations of the committee. The division director should not sit next to the committee chair. Other agency personnel should be placed so that a demarcation between committee members and FDA staff is apparent.

Closed Deliberations

Many advisory committee members, both past and present and including those serving on the IOM committee, those interviewed by the committee, and others, have voiced the complaint that they are always required to function "on stage" and without the opportunity for closed discussions. The preference for the latter stems most often from a desire of scientists to engage in critical, often vigorous back-and-forth technical argument, which is impeded and often thwarted by the constraints of a televised, open meeting before an audience of several hundred individuals.

Regrettably, from the standpoint of facilitating scientific deliberations, the requirements of FACA and the Government in the Sunshine Act make it impossible to close committee meetings save except in defined circumstances. These include the discussion of proprietary information or, on occasion, confidential information about individuals.

CUSTOM TAILORING OF COMMITTEE MEMBERSHIP

As indicated in Chapter 3, the CDRH reorganized its advisory committee system in 1990, formally disestablishing 17 committees and reconstituting them as panels under a single Medical Devices Advisory

Committee. Subsequently, the combination product requirements of the Safe Medical Devices Act of 1990 led the FDA to issue product jurisdiction regulations in November 1991; in that same month it announced three inter-center agreements on the same subject. These efforts led to a rechartering of both the CDER and CBER advisory committees, a process that is being completed this year.

Under these new arrangements, each of these three centers will have the authority to draw needed experts from a long slate of committee members to serve as full voting members at specific panel meetings. This policy is intended to minimize the difficulties of assuring a quorum, to minimize conflict-of-interest problems by expanding the pool from which advisory committee members are drawn, and to allow a better match of expertise to agenda items.

In addition, however, these actions may engender a tension between increased flexibility to match expertise to need and the possible appearance of agency efforts to choose members of an advisory committee to achieve a desired outcome. On the one hand, the Industry Liaison Panel recommended the creation of a large pool of experts on whom FDA could draw for advisory committee members as a means to ensure a match between expertise and agenda item. This proposal reflects the view that the competencies sought on an advisory committee are often specific to a given agenda.

On the other hand, composing an advisory committee from a larger pool of members, however that pool is constituted, is not without problems. Building an advisory committee around a specific agenda leaves the agency open to accusations that the agency is manipulating the committee to achieve a desired outcome. Given, however, that the committees are only advisory and that the FDA is not bound by their advice, the argument that the FDA would deliberately construct a committee around a specific point of view is not compelling.

The IOM committee commends the agency for its rechartering of the CDRH, CDER, and CBER advisory committees to permit greater flexibility in composing a committee in which expertise is related to the subject matter of the agenda. However, the IOM committee also urges care in composing committees from the larger pool of available members.

The IOM committee recommends that, in instances in which the FDA must modify the composition of an advisory committee by "custom tailoring," it do so judiciously and sparingly, augmenting the core committee by adding the needed expertise. The committee also recommends that the FDA actively consult the committee chair in the

process. In addition, it recommends that the director of the appropriate FDA center approve all such decisions.

MEETING FOLLOW-UP

Advisory committee members frequently complain that FDA provides no feedback to them on the results of their deliberations. They have no direct knowledge of the effect of their contributions and, in some measure, regard their input as diminished as a result.

The FDA does not strongly defend its current practice. It often notes that resource limitations on professional staff prevent it from fulfilling this function adequately. It also notes that the progress of an NDA approval is closely followed by the financial investment community, and simple prudence argues against informing committee members of a forthcoming approval in advance of notifying a sponsor.

The IOM committee recommends that the FDA follow up each advisory committee meeting as follows: routinely and immediately provide committee members with a copy of all press releases issued after a committee meeting; inform members by FAX at the time of decision about the approval or disapproval of any application that the committee has considered; routinely report on the status of matters previously considered by the committee at the beginning of each meeting; and report annually the disposition or committee-related matters.

NOTES

1. Memorandum from Bruce Burlington, M.D., Deputy Director for Scientific and Medical Affairs, to Carl C. Peck, M.D., Director, and Gerald F. Meyer, Deputy Director, Center for Drug Evaluation and Research, "Advisory Committees: : Policy and Practices in Selection of Agenda Items To Be Considered by Center for Drug Evaluation and Research Advisory," September 1991.

2. Memorandum from Robert J. Temple, M.D., Director, Office of Drug Evaluation I, to Richard A. Rettig, Institute of Medicine, "Comments on the Industry Liaison Panel to the IOM Committee to Study the Use of Advisory Committees by the FDA," July 8, 1992.

3. Letter from Margaret Jane Porter, Chief Counsel, Food and Drug Administration, to Richard A. Merrill, Professor, School of Law, University of Virginia, June 24, 1992.

4. Kutak, Rock & Campbell. FDA Safeguards Against Improper Disclosure of Financially Sensitive Information. Final Report (Washington, D.C., November 14, 1991).

5. Memorandum from Albert P. Williams, Ph.D., to Richard A. Rettig, "Better Use of FDA Advisory Committees Through Voting Rules," March 10, 1992.

6. Op. cit., Memorandum from Robert J. Temple to Richard A. Rettig.

8

Organization and Management

The IOM committee was asked to consider ways of improving FDA management of, and accountability with respect to, the advisory committee system. In this chapter, the committee examines several issues of organization and management of FDA advisory committees that have been raised by this study. Many of these issues have surfaced in prior reports. In 1990, for example, the Lasagna Committee report recommended "a fundamental restructuring of [the advisory committee] system. The committees should have their own independent staff and should be appointed by, *and report directly to, the Office of the FDA Commissioner* [emphasis added]."

The Industry Liaison Panel recommended a somewhat different approach:

> We believe that the committee system must be enlarged, that more formal training of committee members and executive secretaries should be instituted, and that guidelines should be developed so that each FDA Division operates its committees under the same principles. *To accomplish this a strong central office for committee management is required. To assure uniformity and adherence to established policies, this office should handle both drugs and biologics. The industry liaison panel feels that statutory differences between drugs and biologics on the one hand and medical devices on the other are such that it may be more appropriate for medical devices to be managed separately* [emphasis added]. However, many of the policies, procedures and training programs would be applicable to medical devices as well as drugs/biologics. The industry liaison panel recommends that uniform procedures be utilized where possible.

These different proposals, along with other inputs received by the IOM committee, highlight the need to address issues of organization and management. This chapter, therefore, considers the management of the

advisory committee system, the compensation of advisory committee members, their orientation and training, and suggestions that FDA create advisory committees in addition to its technical committees.

SYSTEM MANAGEMENT

The IOM committee, as it examined ways to improve the management and accountability of the advisory committee system, concluded that a necessary part of its work was to consider how the FDA currently supports and manages this system. It found few prior reports or current assessments that identified the key FDA players and specified their respective roles. This section considers the relationships among advisory committees and the Commissioner and his office, the center directors, the office and division directors responsible for product evaluation, and the executive secretaries. Its purpose is to clarify the roles of these respective officials in advisory committee management.

The Commissioner and His Office

FDA advisory committees are formally chartered by the Commissioner of Food and Drugs to advise him in the discharge of his responsibilities related to ensuring the safety and effectiveness of drugs, biologics, and medical devices for human use. Thus, the de jure reporting relationship of advisory committees to the Commissioner is not in question.

The IOM believes that the authority to create technical advisory committees should be vested in the Commissioner of Food and Drugs (and not in any higher official) and that the formal reporting responsibility of advisory committees to the Commissioner is appropriate. However, as a practical matter, it is not feasible for committees to convey their advice to the Commissioner directly, save on a few occasions of his choosing. Commissioner Kessler, who may have attended more advisory committee meetings than any of his predecessors (perhaps more than all of them together), indicated at the initial meeting of the IOM committee that it was not feasible for advisory committees to report directly to him on a regular basis. Advisory committees usually report to the director of the product evaluation office and to the director of the responsible reviewing division, the significance of which is examined below.

What is the role of the Commissioner? The IOM committee believes that the Commissioner must set the tone for all agency personnel regarding the importance attached to the effective performance of FDA advisory committees. He should also communicate forcefully to advisory committee members themselves, to academic medical scientists, and to the regulated

industries, both formally and through all informal means available, the importance that the FDA attaches to this form of public service, which benefits the public health of the nation.

The IOM committee has also concluded that the Office of the Commissioner has a distinct role to play in the FDA advisory committee system. The advisory committee system has increased in use, in importance, and in public visibility in recent years. Moreover, enough controversies involving advisory committees have occurred in the past two years to justify continuing attention by the Office of the Commissioner. During this time, however, there has been no high-level official in the Office of the Commissioner with a designated responsibility for agency-wide policy and management guidance for advisory committees. The IOM committee concludes that this deficiency should be remedied.

There are three units in the Commissioner's office involved in advisory committee matters, two with administrative responsibilities, and one in policy. The Office of Committee Management prepares the annual report on advisory committees that is required by the Federal Advisory Committee Act (FACA). The Division of Ethics and Program Integrity, as discussed in Chapter 6, reviews initial committee nominations for conflict of interest and also processes conflict waiver requests. Neither entity provides, nor is equipped to provide, policy guidance to the various centers with respect to the advisory committee system. The advisory committee functions of each should be consolidated under the authority of the policy official recommended here.

The Office of the Ombudsman, however, has been recently created (1990) within the Commissioner's office. It deals with specific complaints involving, among other subjects, advisory committees. The Ombudsman has also been responsible for product jurisdiction and combination product regulations, the related intercenter agreements, and the rechartering of CDER and CBER committees that resulted.

Early in his tenure, Commissioner Kessler initiated a reorganization that included the creation of five deputy commissioners (or their equivalent) in the Commissioner's office. These were deputies for operations, policy, and external affairs, a senior adviser for management, and a science adviser to the Commissioner. Notably, the directors of all FDA centers, including those for drugs, biologics, and medical devices, now report to the Deputy Commissioner for Operations.

What advisory committee system functions might be performed by the Office of the Commissioner? In the judgment of the IOM committee, a need exists for clear policy and management guidance to the FDA advisory committee system from the Commissioner regarding the role, importance, and general operations of advisory committees in the work of the agency.

Specifically, the following potential tasks might be considered as appropriate:

- monitor the performance of the advisory committee system for the Commissioner;
- exercise leadership in standardizing committee procedures and reducing unjustified variation wherever feasible;
- coordinate agency-wide advisory committee functions;
- oversee the computerization of committee processes;
- monitor charges of "undue influence" of FDA over advisory committees;
- articulate policy and monitor performance of the recruitment of advisory committee members, especially women and minorities;
- coordinate conflict-of-interest policies and procedures affecting advisory committees on behalf of the Commissioner, and negotiate with the DHHS Office of the Special Counsel for Ethics and the Office of Government Ethics on the agency's behalf;
- review all existing regulations, forms, and implementing documents pertaining to advisory committees and revise them as appropriate;
- revise and update the Staff Manual Guide; and
- exercise leadership in the development and implementation of an orientation and training program for the advisory committee system.

The above functions deal with policy and management issues; they are not intended to involve the day-to-day operations of the advisory committee system.

The IOM committee regards the specific organization of the Office of the Commissioner as the province of the Commissioner. However, given that all FDA centers, including the three of concern in this study, report to the Office of the Deputy Commissioner for Operations, it regards this office as the most likely location for a high-level advisory committee function.

The IOM committee recommends that a high-level official in the Office of the Commissioner of Food and Drugs be assigned primary responsibility for developing, disseminating, enforcing, and monitoring administrative policy and management guidance to the advisory committees of the three centers.

Center Directors

The current directors of the three centers all strongly support the advisory committee system, although their involvement in the work of the

committees varies. The roles of the center directors are not spelled out with respect to advisory committees, however, and the IOM committee has concluded that this kind of clarification would be useful.

What functions might center directors be formally expected to carry out with respect to advisory committees? The following are important:

- ensure implementation in their respective centers of agency-wide policy toward advisory committees developed in cooperation with the Office of the Commissioner;
- monitor the recruitment of advisory committee members for expertise, external endorsement, and special efforts to recruit women and minority members;
- review all "custom tailoring" advisory committee meetings that involve matching the composition of the committee to the technical requirements of an agenda to avoid charges of "undue influence";
- help design an orientation and training program along the lines recommended below;
- examine issues that may arise in the work of one or several advisory committees that may cut across the work of the entire center and require consideration on a broader basis than a single committee (or division) can provide; and
- support innovation in the use of advisory committees.

Office and Division Directors

The role of advisory committees cannot be specified clearly without clarifying the management responsibility for advisory committees within the FDA. The executive secretaries are often identified as the key FDA officials responsible for advisory committees. Although this is true for administrative support purposes, it is not generally true for the substantive work of the committees.

Authority for product approval of new drugs, biologics, and medical devices is vested in the Commissioner, then delegated to other FDA officials. In CDER, authority is delegated to the center director, then to the directors of the two offices of drug evaluation; in the case of oncology drugs, the delegation is one step downward to the division director for oncology and pulmonary drug products. The working responsibility for product evaluation and operational responsibility for approval resides within the three centers at the level of the division director. Thus, in substantive terms, the primary responsibility for management of advisory committees resides with division directors.

Advisory committees exist to provide independent expert advice to the FDA, primarily to the FDA officials who approve or disapprove applications. It is important, therefore, to clearly state that the relationship between office and division directors, on the one hand, and advisory committees, on the other, must be a comfortable, productive working relationship based on mutual respect and a commitment to scientific assessment of new therapeutic products. Clarifying this relationship is important both for internal administrative purposes and for external "consumption."

The role of the division directors in advisory committee management should include, at a minimum, involvement in the recruitment of advisory committee members, preparation of the committee agenda (with the advisory committee chair), and preparation of the specific questions that the committee is asked to consider (also with the chair).

Executive Secretaries

Executive secretaries have both administrative and substantive roles to perform in the advisory committee system. The primary administrative role should be to promote the efficient performance of an advisory committee. (By extension, the organization of the executive secretariat should be to promote the efficient operation of the system.) Specific functions of executive secretaries include recruiting committee members and preparing nomination packages; administering conflict-of-interest reviews on initial appointment and processing waivers for specific meetings; arranging meeting logistics (whether on an internal or contract basis); distributing materials to advisory committee members; and following up committee meetings.

The administrative work of the executive secretaries intersects with the substantive agenda that the reviewing offices and divisions wish to bring before an advisory committee. This may involve participation in formulating the agenda of a given advisory committee meeting, determining the appropriate sponsor and FDA materials to be sent to the committee, and preparing the questions that the committee is being asked to consider.

Currently, CDER is organized with most executive secretaries assigned to a central unit but with some assigned to reviewing divisions. CBER also has a central executive secretariat. CDRH assigns professionals from reviewing divisions to serve, in addition, as executive secretaries. Executive secretaries in CDER and CBER are engaged in the support of advisory committees on a full-time basis. CDRH executive secretaries, however, are usually professional staff involved in product evaluation; thus, they are engaged in the substantive work of advisory committees, as well as providing administrative support.

Given these administrative and substantive responsibilities, the Industry Liaison Panel recommended a dual reporting arrangement whereby the executive secretaries report to a centralized unit within each center for administrative support of advisory committees and also to the directors of the reviewing divisions for substantive support. The IOM committee concurs in this recommendation.

The organization of the executive secretaries is an issue that has a long history within FDA, the focal point of which has been the centralization of the executive secretariat. The term has several meanings. One meaning is centralization at the level of the three respective centers, which is the prevailing pattern. A second meaning is a consolidated committee management staff that serves both drugs and biologics, while leaving CDRH with its distinctive system of committee management. Finally, the term *centralized* can be extended conceptually to include CDER, CBER, *and* CDRH, although this has never been done and has not been seriously advocated.

Historically, the second meaning derives from 1982 when the organizational units responsible for drugs and biologics were merged into a single center. A centralized committee management staff was created at that time, and this arrangement continued beyond the 1987 reorganization that split drugs and biologics into CDER and CBER. In 1991, the committee management unit was finally split into separate units for the respective centers.

The IOM committee believes that the primary function of the center-based executive secretariat should be to provide the administrative and logistical support of advisory committees. Efficiencies can be achieved as executive secretaries learn from each other. However, the argument for a consolidated CDER and CBER unit rests, in part, on a philosophy that an executive secretariat should have some autonomy from the reviewing divisions and should be responsible for managing the advisory committee system to ensure the independence of the advice provided by advisory committees.

The IOM committee believes that guaranteeing the independence of the advice provided by advisory committees cannot be done through the executive secretariat, however it may be organized. Rather, it requires the diligence of center directors and policy oversight by the recommended high-level official in the Office of the Commissioner.

The IOM committee recommends that the executive secretaries report to a central unit in their respective centers for the purpose of providing administrative support to that center's advisory committees. It also recommends that they report to the appropriate division directors to provide program support to the committees.

In general, the IOM committee believes that a clarification of the roles of all FDA officials responsible for the advisory committee system is long overdue. The objective of this clarification should be to ensure that advisory committees provide the independent expert advice that the agency requests and needs.

The IOM committee recommends that the roles and responsibilities of all FDA officials involved in the advisory committee system be clearly articulated in agency policy that is widely distributed to FDA professional staff, advisory committee members, and other interested parties. The committee further recommends that the job descriptions of all officials be changed to reflect their respective responsibilities.

COMPENSATION

The authority to set the daily rate of compensation for FDA advisory committees resides with the Commissioner of Food and Drugs. He is subject to four constraints—two legal, one budgetary, and one administrative.

The statutory limit on compensation for *all* federal government advisory committee members is the daily rate for a Senior Executive Service IV position, currently $429.50 per day. Regulations of the General Services Administration further limit the daily rate to that of a GS-15 in the General Schedule, currently $320 per day, unless the agency head personally determines that a higher rate "is justified and necessary." The budgetary limit is the obvious requirement that an agency head must have funds to cover the costs of whatever rate is adopted.

Although agency heads have authority to set rates for the members of the committees that advise them, FDA's status as a part of the Public Health Service also limits that authority. As a practical matter, no single PHS agency can pay advisory committee members at rates much higher than those of the other agencies. Currently, the Centers for Disease Control pays committee members $188 per day, the National Institutes of Health pays $150 per day, and the FDA pays $150 per day.[*]

[*] In 1965, advisory committee members for drugs and biologics were paid $128.80 per day. This rate was lowered in 1984 to $100; it was raised to $150 in February 1990. Device committee members were paid $128.80 per day from 1972 until this rate was raised to $150 in 1990. Using the Consumer Price All-Items Index to inflate and deflate these figures, the $128.80 fee translates into $572.67 in 1992 dollars; conversely, $150 in 1992 dollars is the equivalent of $33.63 in 1965 terms. Members of the Edwards Committee, incidentally, who were appointed by the Secretary of Health and Human Services in 1990 to advise on matters pertaining to the FDA, were paid approximately $300 per day.

FDA advisory committee members are paid only for those days on which they attend a meeting. The agency is barred by regulation from paying them for homework for normal meeting preparation, even though an individual may spend five days or more in preparation. However, CDRH does compensate individual advisory committee members for homework if they conduct an "agency-directed assignment" that results in a tangible end product, usually a report, that is not the end product of the advisory committee. Typically, this involves using members as primary reviewers of applications. Neither CDER nor CBER compensates committee members for homework.

FDA regulations also permit payment to advisory committee members at the daily rate for travel time that involves 50 percent of an additional day beyond the meeting and that results in the loss of some regular compensation. However, no use is made of this authority.

The IOM committee believes that all Public Health Service advisory committee members are underpaid, including those who advise the FDA. This is clearly true with respect to the maximum daily rate allowed by law and GSA regulations. It is also true with respect to the opportunity cost to members of foregone consulting fees from drug or device firms of $1,000 a day or more. Moreover, younger members in academic medicine often confront the perception that service on an FDA committee carries less academic reward than that of an NIH study section.

The IOM committee believes that public service should be adequately compensated, although obviously not at the rates found in the private sector. It is concerned that the current meager rate of compensation may dissuade some individuals from serving as FDA advisory committee members and may diminish the incentive to others to prepare adequately for meetings. In general, the IOM committee is concerned that these rates do not adequately reflect the value that FDA and the general public attach to the important work performed by advisory committee members.

The IOM committee recommends that the Commissioner, with the Secretary of Health and Human Services, review the adequacy of compensation for Public Health Service advisory committee members, including FDA advisory committee members, and take appropriate steps to maintain daily rates in relation to increases in the federal salary schedule. It further recommends that CDER and CBER, to the extent that they use primary reviewers for applications presented to advisory committees, compensate these reviewers, as CDRH currently does, for "agency-directed" homework.

The IOM committee notes that legislation enacted in October 1992 authorized the FDA to charge user fees for product evaluation. Under this new authority, it may be appropriate for the FDA to review the compensation of advisory committee members in relation to their contribution to product evaluation.

ORIENTATION AND TRAINING

Insufficient orientation of advisory committee members is a recurring complaint. It was raised by the Industry Liaison Panel report and in the interviews of current and former advisory committee members conducted by a working group of the IOM committee. Many—perhaps most—of these past and present advisory committee members felt that their training and orientation had been inadequate. Several still had only a vague knowledge of the structure of the FDA and the committee's relation to it—which raises questions about their understanding of their roles and responsibilities. Some suggested a more formal orientation (perhaps using audiovisual materials and a new orientation manual), and a significant number argued for a clearer statement of the committee's role in FDA functions.

Among the critical comments of those interviewed were these: "It's like being a trial lawyer without ever being in the courtroom!" and "[Orientation was a] 30-minute phone call and a written folder." There were also, however, some positive comments: "I feel that the training and orientation session was superb. It may be reasonable to repeat some of the basic principles periodically.... [For new members] I might suggest ... that there also be direct contact with the immediate predecessor."

The following were among the specific recommendations for improving orientation of committee members:

- A one-day training session for new members before the meeting of an advisory committee.
- Having new committee members attend a meeting before becoming an active advisory committee member.
- An hour-long closed session to introduce new members to the issues. This should be at the first meeting of the new group and should include seasoned committee members so that they can answer any questions raised by new members.

The training and orientation of advisory committee members and agency staff were addressed in both the Dorsen report (1977) and the McMahon report (1982). Both studies found, after interviewing committee members and FDA staff, that a lack of preparatory information led to frustrations

among committee members. Furthermore, because of a lack of advance information about the precise duties of members of advisory committees, many experienced disappointment as they discovered that certain decisions required of the committees could be more mundane than they had originally expected.

The need for a systematic orientation program is generally recognized throughout the agency. Among advisory committee members, one encounters the belief that a more systematic orientation and training program is needed, especially for new members, who reportedly often come to the initial committee meetings without knowing what is expected of them or how FDA exercises its regulatory responsibilities. As a result, they are not always prepared to play an effective role until well into their term.

The need for orientation and training appears to be widely recognized; what, then, has been the agency response? One response was the preparation of a handbook entitled *FDA Public Advisory Committees: A Handbook for Advisory Committee Members and the Executive Secretary*, which is routinely distributed to prospective CDER and CBER advisory committee members. Some committee members have reported to agency staff, however, that the handbook does not provide them with the background they need to perform their tasks. CDRH has prepared a videotape on the duties and responsibilities of advisory panel members and distributes it to all of its prospective committee members.

Responsibility for training advisory committee members is decentralized to the respective centers, usually to individual executive secretaries or committee management staff. The staff of the three centers do not meet to discuss the training needs of committee members or to collaborate in developing orientation programs. Moreover, neither the Division of Human Resources Management, which designed FDA's training programs until about 10 years ago, nor the training staffs of the centers have been involved with the orientation of advisory committee members. Consequently, orientation varies greatly between centers and often within a given center—from day-long and half-day orientation sessions to committee member "apprenticeships" as consultants and "on-the-job" training of members.

In CDER, no single individual supervises the orientation of advisory committee members. Each committee's executive secretary is responsible for whatever orientation is provided. Although the executive secretaries who are part of the Advisors and Consultants Staff share information on how to orient new members, there are no meetings of all CDER executive secretaries to discuss orientation or to develop a consistent CDER approach. However, all prospective committee members are given written information on conflict of interest. The handbook, relevant regulations, and committee

charters are often included in the orientation packages prepared by individual executive secretaries, and division-specific materials are sometimes also provided to new members. But there is no standard set of materials provided to new members.

Direct personal orientation of advisory committee members is also left to the discretion of the executive secretaries. (One CDER executive secretary expressed the view that the interests of the members of CDER's 17 advisory committees varied too much to hold one orientation session.) Several approaches are used. If a number of members at a given advisory committee meeting are new, part of the meeting may be closed for orientation. Another option is to hold an orientation session the evening before an advisory committee meeting or to ask a single new member to stay an extra day after a meeting.

CBER's two executive secretaries are also responsible for orienting new committee members. In March 1992, however, its Division of Scientific Advisory Committees conducted a pilot orientation session to improve its orientation program, which was attended by new members from all four CBER advisory committees. This program is still in its formative stages and, as currently planned, consists of a morning plenary session that covers topics of interest to all committee members (e.g., ethics, proprietary information, personal liability, etc.) and a specialized afternoon session for each committee for its own new members. It has not been decided whether to schedule sessions the day before a new member's first advisory committee meeting or to hold a separate event for all new members.

Of the three centers, CDRH has the most structured orientation program for new advisory committee members. Like CDER and CBER, new advisory committee members receive written materials that explain their responsibilities. In addition, however, the Advisory Panel Coordinator (APC) within the Office of Device Evaluation asks an executive secretary in advance of a panel meeting if there are any new members located in the Washington, D.C., area. Currently, cost prohibits bringing in out-of-town panel members for orientation. If so, an orientation session will be scheduled for these individuals, and the other executive secretaries will be asked to identify new panel members in the area who should also attend.

The purpose of the training is to discuss the relationship of the written materials provided to the new panel members to the CDRH regulatory context. In this way, panel members can focus their attention in the most productive and appropriate way possible. The two-hour orientation session is sometimes scheduled immediately before a panel meeting begins or sometimes on the previous day. The CDRH executive secretaries provide feedback to the APC from both the divisions and the panel members. If

either sees deficiencies in the orientation, the executive secretaries convey that information to the APC.

CDRH has also prepared three videotape scripts for use in orienting new panel members. These deal with "Mission & Organization"; "Medical Device Approval: The Process & The Panel's Role"; and "Avoiding Conflict of Interest." The idea of training videos for panel members was developed by the Office of Device Evaluation and the Health Industry Manufacturers' Association (HIMA), and scripts were written by a contractor (who was paid $10,000 by HIMA). CDRH provided a great deal of input, and the scripts were approved by the center in 1991. The project is currently on hold while CDRH awaits word on whether HIMA wishes to continue, whether the center has the funds to do so,* and whether their plans will accord with the recommendations of this study.

The centers also use other means of orientation. A division will sometimes invite a potential new member to a meeting as a guest to acquaint them with the advisory committee process. Or it may hire the person in a consultant capacity as an "apprentice" committee member, which serves the dual purpose of giving the division an opportunity to evaluate an individual's potential as a committee member and giving the individual some familiarity with the work of a member.

What questions deserve attention in considering a more systematic orientation and training program for advisory committee members? First, the rationale for such an effort is straightforward: systematic orientation and training of advisory committee members would fulfill a widely recognized need; it would promote the efficient use of committee members' talent; it would establish clear expectations for members about their roles and responsibilities; and it would permit agency officials to explicitly acknowledge the important public service contribution of advisory committee service.

In addition, were the program agency-wide, it might encourage "soft standardization" across the three centers. It would do so by promoting concern for common problems without overriding the justifiable variation that derives from a particular class of therapeutic or diagnostic entities. If the effort was developed by the Office of the Commissioner in concert with the centers, it would force clarification about how much the content of such a program should be agency-wide, center-specific, or specific to a given division or class of therapeutic products.

What should be the content of an orientation program? The answer to this question should be developed by the appropriate FDA staff in conjunction with selected advisory committee members. The content

* Estimates to produce the videos range from $10,000 to 25,000 each, depending on whether professional actors are used.

criterion should be what a new member needs to know to be effective as a committee member. It should probably include a description and some history of FDA's statutory regulatory responsibilities; a discussion of the purposes of FDA advisory committees, including how they differ from NIH study sections and other similar committees; a careful and sensitive examination of the conflict-of-interest law and its implementation; and the important public service and public health contribution of advisory committee work. New committee members would also benefit from a discussion of the "Format and Content' guidelines for submission of a new drug application prepared several years ago by Drs. Robert Temple and Robert O'Neil.

A related need is the orientation of advisory committee chairs to their roles, which none of the centers do routinely; their orientation should include FDA policies and procedures regarding electronic coverage of advisory committees (21 CFR 10(200–206)). Furthermore, assuming that recommendations of this report about strengthening the role of committee chairs are accepted, orientation could usefully focus on these enlarged responsibilities.

Should the scope of an orientation and training program be restricted to advisory committee members, or should it also include the training of FDA officials who routinely deal with advisory committees? Although the initial emphasis should be on members, a well-designed program should serve both groups.

What kind of orientation and training materials should be used? At a minimum, a current orientation manual should be prepared (and maintained) for all advisory committee members. In addition, a videotape should be prepared to capture the views of the FDA Commissioner and relevant high-level FDA officials regarding the importance of the advisory committee function. Finally, a program of face-to-face, one-day sessions should be held for new committee members.

Across the three centers, approximately 75 new advisory committee positions become open each year. If an agency-wide program was designed, with content that was agency-wide, center-specific, and division-specific, one or two annual sessions could be organized for all new members from all centers.

Potential organizations responsible for conducting an orientation and training program include the FDA Division of Human Resources; center-level units, such as the CDER Staff College or the CDRH training office; an agency-wide effort jointly organized by the three centers; or an external contractor. The specific design is an administrative choice to be made within the agency after the basic parameters of the program have been established.

The IOM committee recommends that the FDA establish a systematic orientation and training program that is directed mainly toward new advisory committee members, with a special component for committee chairs, and that will also be useful for current members and for FDA staff who deal with committees. The Office of the Commissioner should exercise leadership in the design of this program, in cooperation with the three centers. The design should consciously search for agency-wide similarities as well as center-specific and division-specific content. The public service and public health contribution of advisory committee membership should be emphasized in this program.

TYPES OF ADVISORY COMMITTEES

The IOM committee has focused its attention in this report on the technical advisory committees used by the FDA for drugs, biologics, and medical devices. In the course of the study, however, several suggestions have been made that the committee consider other types of advisory committees and these are reviewed briefly in this section.

Policy Advisory Committee

The first issue was whether the IOM committee should recommend that a policy advisory committee be established to advise the Commissioner on the broad policy issues related to drugs, biologics, and devices that come before the agency. The Lasagna Committee, for example, recommended formation of "a permanent standing Policy and Oversight Committee ... to monitor the agency's needs and performance with regard to regulation of drugs and biologics for humans." It proposed that this committee meet regularly and report to the Secretary of Health and Human Services; and that its members be "knowledgeable national leaders" selected by the Secretary from candidates nominated by the Institute of Medicine.

The IOM committee discussed this issue at its December 7, 1991, meeting and again at its meeting on May 29–30, 1992, but on neither occasion was any great enthusiasm for such a committee noted. Instead, the committee observed that the Commissioner of Food and Drugs, like the head of any government agency, does not lack for free advice from many sources. It concluded that the utility of such a policy advisory committee should be determined by the Commissioner, who can ask the Secretary to appoint such a body if it would serve his purposes.

The committee did hear a presentation from the newly appointed Science Adviser of the FDA, Dr. Elkan Blout, regarding his plans for the creation of a science board. This board, when chartered, might fulfill some

of the functions envisioned for a policy advisory committee to the Commissioner.

Other Issues

Several other issues were raised late in the IOM committee's study. First, the committee received suggestions that cross-cutting, discipline-based advisory committees (in contrast to the therapeutic class or product-line technical advisory committees) be established for biostatistics, chemistry, pharmacology and toxicology, and biomaterials.[1,2] The basic rationale for such an action was that existing committees often raised issues in product evaluations that had broader implications than those related to a given application. No advisory committee exists for aggregating and considering such issues.

Currently constituted technical advisory committees focus on product evaluation, broadly construed. The membership of such committees usually includes representatives of several critical, cross-cutting disciplines to provide valuable perspectives; biostatistics is almost always represented; and chemistry and pharmacology\toxicology are sometimes included. However, discipline-based issues that arise within product-oriented advisory committees and that have center-wide or agency-wide implications are not systematically examined. We note, however, that the substantive issues that such committees might address could very well be candidates for technical workshops that the agency, or one of its centers, might sponsor, perhaps drawing participants from the membership of existing advisory committees.

Two other issues were raised with the committee. Should each of the three centers have a policy advisory committee? And should CBER establish a "board of scientific counsellors" to review all its intramural research programs and personnel, rather than divide that responsibility as it currently does, among four technical advisory committees?

All these issues were raised late in the IOM committee's study. Although they merit discussion and debate, the committee did not have extensive opportunity to consider all of their implications. It regards all of these matters as appropriate subjects for internal FDA discussion and decision. The IOM committee wishes to note that if the FDA adopts its recommendation that the agency establish a high-level position within the Office of the Commissioner for advisory committee policy and management guidance, the framework would exist within which such issues could easily be considered.

AGENCY MANAGEMENT AND ACCOUNTABILITY

This report makes many recommendations for improving the use of advisory committees by the FDA in the evaluation of drugs, biologics, and medical devices. Throughout the report there are general expressions of concern about agency management and accountability, which may not be captured fully by the report's specific recommendations. Thus, the IOM committee deems it necessary to summarize the latter in relation to these larger considerations.

Agency Management

In the judgment of the IOM committee, it is important to differentiate between the management of the advisory committee system and the management of the product evaluation process as affected by the advisory committee system. Regarding system management, the IOM committee's most important recommendation is that a high-level position be established in the Office of the Commissioner to provide administrative policy and management guidance to the advisory committee system. Although the precise location of such an office is properly a decision to be made by the Commissioner, an appropriate place may be the Office of the Deputy Commissioner for Operations, to which the directors of the three relevant centers now report.

Advisory committees, the IOM committee believes, have become a permanent fixture in the FDA's evaluation of products, and their effective use should be a responsibility of FDA officials at all levels. Improvements in management would flow from clarifying the roles and responsibilities of all officials involved in the advisory committee system from the Commissioner through center, office, and division directors, down to the executive secretaries. Such clarification should include expanding the job descriptions of these officials as necessary. The IOM committee acknowledges the important role of FDA office and division directors in the work of advisory committees; it does not recommend circumventing these officials by proposing to locate operational responsibility for committees elsewhere, but urges clarification of their responsibilities for the effective performance of the system.

An orientation program for advisory committee members, which could also be used in training responsible FDA officials, would improve the performance of the entire system. Other management-related recommendations pertain to the recruitment of qualified members and establishment of a pool of potential members; greater involvement by the Office of the Commissioner in conflict of interest issues (both in developing internal FDA

policies and procedures and in negotiating with the DHHS Office of the Special Counsel for Ethics and the Office of Government Ethics); and more attention to preparation for and conduct and follow-up of advisory committee meetings.

Various recommendations of the IOM committee address improvement of the product evaluation process and the role of advisory committees in that process. In particular, we believe that advance scheduling of committee meetings and agendas, with attendant deadlines for the sponsor and the agency, would bring greater discipline to the product evaluation process.

The IOM committee recognizes that its recommendations for improved management of the advisory committee system will require additional resources. Therefore, the report provides an estimate of the incremental costs of the IOM committee's recommendations. The IOM committee regards the recommended review of advisory committee member compensation as an important management issue that deserves attention by the Commissioner and the Secretary of Health and Human Services. If a user fee system is adopted to support product evaluation, the compensation of advisory committee members should be reviewed in that context.

Agency Accountability

The FDA as an entity, and not its component parts, should be accountable for the effective performance of its advisory committee system. The IOM committee's recommendations lead to ways of increasing agency-wide accountability. Here, as in the recommendations above on improving management, the committee emphasizes the importance of designating a high-level official in the Office of the Commissioner who should be responsible for administrative policy and management guidance for the system.

It is also important as a component of accountability to recognize that advisory committees are *advisory* to the FDA, and that the formal authority for decisions rests by law with the agency. It would be unnecessary to reiterate this basic distinction were it not that some agency critics regard advisory committees as independent adjudicatory bodies that should hear sponsors' views, on the one hand, and agency views, on the other, and decide in favor of one party or the other. Acknowledging this basic authority-advisory distinction should facilitate advisory committees becoming even more effective and influential than they are at present, which the IOM committee endorses.

Consequently, the IOM committee's recommendations emphasize practical ways (especially in Chapter 7) to ensure the intellectual independence of advisory committees. The rationale for this emphasis is to increase

the likelihood that advisory committees will render that impartial, expert advice that the agency and the public should expect.

A CONCLUDING RECOMMENDATION

In the conduct of this study, the IOM committee has discovered the multifaceted complexity of the FDA advisory committee system. It has benefited from many thoughtful letters, memoranda, and communications on aspects of this complexity. The committee has blended these views of others, both inside and outside the agency, with the knowledge and experience of its members and with the information gained in this study. As a result, the committee believes that its report, if widely disseminated, could serve to increase both internal agency accountability and external support for the advisory committee system.

The IOM committee recommends that the Commissioner circulate this report widely within the FDA, to all advisory committee members, and to other interested parties. It also recommends that the report be submitted to the Secretary of Health and Human Services and to the appropriate committees of the Congress for the purpose of seeking concurrence of goals and budgetary support for the implementation of the report's recommendations.

NOTES

1. Letter from Lewis B. Sheiner, M.D., University of California, San Francisco, to Richard A. Rettig, May 4, 1992.

2. Letter from John F. Beary, III, M.D., Pharmaceutical Manufacturers Association, to Richard A. Rettig, May 20, 1992.

Appendix A

Resource Implications*

The implementation of the IOM committee's recommendations in this report does not depend greatly on additional budgetary and personnel resources. Many recommendations involve policy determinations that will lead to procedural changes. The one-time "costs" of the former will be absorbed by the agency's review of this report. The procedural changes, the committee believes, will result in greater effectiveness of the advisory committee system; some may also result in increased efficiencies.

This Appendix identifies five recommendations (or sets of recommendations) of the IOM report that will require additional monies or personnel. It provides a first approximation to the resource implications of those recommendations. It does not purport to be a technical cost estimate of all recommendations, as such an effort would require more data than are readily available and would dwarf the study itself. The analysis is preceded by a brief discussion of the costs of the current system.

CURRENT SYSTEM COSTS UNDERESTIMATED

Each year, the FDA prepares an Agency Summary on the fiscal year costs of all of its advisory committees, in compliance with the requirements of the Federal Advisory Committee Act (FACA). This report is the primary source of public information about the costs of FDA advisory committees and its data are used in the agency's budget submission to Congress. Table A-1 summarizes these data for fiscal years 1987 through 1991 in terms of the FDA's cost categories.

The committee management staffs of the three centers compile the data for the annual report in accordance with guidance from the FDA's Committee Management Office. Although most of the cost computations are

* This appendix is based on an analysis prepared by Rebecca Wallace.

Table 1 FDA's Advisory Committee Costs: Fiscal Year 1987 through Fiscal Year 1991

Data Elements	1987	1988	1989	1990	1991
Personnel Payments					
Nonfederal Members	$65,849	$64,193	$77,391	$86,952	$101,963
Federal Staff	441,388	518,484	696,228	733,277	1,141,999
Nonmember Consultants	18,454	24,707	23,145	32,958	32,850
Subtotal	525,691	607,384	796,764	853,187	1,276,812
Total Travel and Per Diem	215,607	270,629	358,242	354,124	397,257
Other	75,815	78,194	113,484	139,235	157,506
Total	817,113	956,207	1,268,490	1,346,546	1,831,575
Total FTE Years	11.90	12.40	17.82	17.00	26.01

Note: FTE = full-time equivalent.

straightforward, there is reason to believe that the reported costs are understated, especially those of personnel payments to federal staff.

First, not all committee management salaries are included. Federal staff costs for all three centers include only those committee management staff who spend 10 percent or more of their time in direct support of advisory committee business. Moreover, CDER figures include only the salaries of executive secretaries and the committee management assistants; CBER payments exclude the secretarial support of its committee management staff. These costs do not include the other members of the committee management staffs. In addition, CDRH costs do not include the costs of a contractor ($95,000 in fiscal 1991) that provides support services to its device advisory committees. Also excluded are the staff of the Division of Ethics and Program Integrity who process conflict-of-interest waivers, and the FDA's Committee Management Office, which prepares the annual report on advisory committees. Beyond these omissions, the costs of division personnel, from medical reviewers through division directors, that might be allocable to advisory committee work are also excluded.

RECOMMENDATIONS THAT WILL HAVE RESOURCE IMPLICATIONS

Five recommendations of the IOM committee, if adopted, will require additional resources for which the incremental costs can be identified and calculated relatively easily. They are: (1) improving the management of the advisory committee system by appointing a high-level official in the Office of the Commissioner to provide management and administrative policy guidance to the system; (2) strengthening the process for recruiting advisory committee members; (3) establishing needed training and orientation efforts; (4) scheduling advisory committee meetings a year or more in advance, and reviewing the NDA and IND pipeline each year; and (5) possibly increasing advisory committee members' compensation.

1. Improving the Management of the Advisory Committee System

The IOM committee recommendation that a high-level position be established in the Office of the Commissioner to provide management and policy guidance for the advisory committee system will require the FDA to devote one full-time senior staff position and at least part-time administrative support to this new function within the agency. Performing the tasks suggested by the panel will require an individual who works closely and on an even footing with center, office, and division personnel.

2. Recruiting Committee Members

The IOM committee recommends that the recruitment process be organized in a systematic, formal, and aggressive way, with special attention to women and minorities. There are three potential sources of cost to increased recruiting efforts. First, it may be the case that one fun-time equivalent (FTE) in each center will be needed to perform the day-to-day responsibilities of recruiting (including routinely soliciting ideas for potential members from current and former advisory committee members; professional medical and scientific societies; medical school deans and department chairmen; and industry, consumer, and patient organizations); contacting appropriate professional journals; using the NIH-ADAMHA computerized file; and communicating with potential committee members to increase their interest in serving on a committee.

Second, if the FDA pursues the option of creating and maintaining its own computerized data base of potential advisory committee members, the agency will incur additional costs. The NIH-ADAMHA system is an example of what such a system might cost. Most of the design and maintenance of this system is done by a contractor, who sends all the mailings, performs all data entry, makes minor program changes, offers six tutoring sessions on the system to the professional staff each year, maintains a users manual, responds to all questions on the system, and duplicates all CVs and provides them to requestors. The contractor is currently designing a program to put all CVs on-line.

Original design costs for this contract are not known but current operating costs are $250,000 per year. The contractor uses one professional to manage the system and two or three staff for data entry and troubleshooting. In addition to the annual contract costs, an NIH project director spends 10 percent of her time monitoring the contract. ADAMHA, through an interagency agreement with NIH, contributes about $50,000 per year to the effort. Contract costs are expected to decrease as the data base becomes more complete and maintenance becomes more routine.

The development of this system required the NIH to obtain clearance from the Office of Management and Budget to ask private individuals for personal data. Special permission was needed to ask for gender and race information. In addition, the NIH had to obtain Privacy Act clearance to store the acquired information.

Third, in lieu of developing its own automated system, the FDA might enter into an interagency agreement to support the NIH system and seek to have it modified to meet its own special needs. The NIH, in August 1992, was forming a task force to recommend changes to the system.

3. Establishing an Orientation Program

The IOM committee recommends that the FDA develop an orientation program consisting of an FDA-wide component, a center-specific component, and a division-specific component. It further recommends that this program be offered two or three times a year and that all new members attend within six months of their appointments. In addition, the committee recommended that the FDA develop a training program for its staff who deal with conflict-of-interest issues; this training effort could provide the basis for the conflict component of the orientation program.

Course development would be an initial cost to the agency, and as FDA policies change, the material would need to be updated. According to an FDA staff member who has developed such programs in other agencies, designing a 3–6 hour course in-house would take about one-quarter of an FTE, or $15,000–$16,000. This amount would depend, of course, on the accessibility of materials and resources needed to develop the curriculum and the ease of reaching agreement on substance among the relevant senior FDA staff from the three centers.

Once the course is developed, the additional costs of conducting the program would include advisory committee member compensation, travel, and per diem; FDA staff time; and space and facilities, supplies, and incidentals. Factors affecting costs include the frequency of orientation sessions, the specific FDA staff who will participate when and where the sessions are held, and what training methodology is used.

If the FDA adopts the IOM recommendation to hold two or three orientation sessions in Washington, D.C., per year, separate from any scheduled committee meeting, new advisory committee members must make an additional trip to Washington. Assuming that one-quarter of the committees' staffs turns over each year, approximately 91 advisory committee members will require orientation each year. The estimated additional compensation to advisory committee members, travel, and per diem each year for 91 members are:

member compensation for 2 days (at $150/day) travel and per diem for 2 days	$27,300, 40,586.

The logistical aspects of the sessions might require four to five days of FDA administrative staff time per session. The amount of professional staff time needed to run the orientation sessions will depend on the extent to which videotapes or other training methods can be used in lieu of face-to-face instruction. At a minimum, one staff member from each center would need to be present for each day of orientation.

Regarding videotapes, the CDRH has approved three video scripts for use in its advisory committee orientation sessions: "Mission and Organization"; "Medical Device Approval: the Process and the Panel's Role"; and "Avoiding Conflict-of-Interest." Although the scripts were prepared by a contractor, significant FDA staff time was involved in providing input, reviewing the scripts, and, in some cases, rewriting them. Funding for the contractor of $10,000 was provided by the Health Industry Manufacturers' Association (HIMA). Production costs will range from $10,000 to $25,000 per videotape, depending on whether or not professional actors are used.

4. Scheduling Advisory Committee Meetings in Advance; Reviewing theNDA and IND Pipeline Annually

The IOM committee recommends that the FDA establish a meeting schedule for each committee one year in advance. These recommendations have cost implications in terms of staff years for both center staff and committee management staff. Staff time within each center will need to be devoted to developing a meeting schedule for all committees one year in advance, and to continually reviewing what is in FDA's pipeline to revise that schedule as necessary.

The potentially most significant additional cost to the agency to implement this recommendation may be the need for more FDA medical reviewers to complete reviews on a scheduled basis. This need is a matter that the agency will undoubtedly wish to examine carefully in its evaluation of this recommendation.

5. Increasing Compensation of Advisory Committee Members

Although the IOM committee does not recommend an increase in compensation for advisory committee members, it urges the Commissioner to raise this matter with the Secretary of Health and Human Services. If the Commissioner does so, and if compensation is increased, there are obvious budgetary implications of such action.

Below we compare the estimated cost to the FDA of three rates of compensation for advisory committee members in fiscal year 1991. These are the current rate of $150 per day and two hypothetical rates of $250 per day and $320 per day. The $250 rate is arbitrary but reasonable; the $320 rate is the maximum currently payable (GS-15, step 10) under GSA rules. The cost computations are based on 899 advisory committee member/consultant reimbursable days.

Rate per Day	Costs
$150	$134,813
250	224,750
320	287,680

If the FDA were to pay for advisory committee members' homework, which it does not now do, save for clinical reviews by CDRH committee members, this would add to the costs of the system. Estimates follow of the incremental cost of allowing five days of homework per committee member (assuming an average of 10 members per meeting) at three different compensation rates, $150, $250, and $320 per day. The incremental costs range from $500,000 to $1 million a year.

Rate per Day	Costs
$150	$480,000
250	800,000
320	1,024,000

The FDA's regulatory responsibilities are vast and the expertise needed to effectively carry them out are equally great. It is neither feasible or desirable to eliminate the use of advisory committees as a way to acquire some of that expertise. Thus, the FDA must commit resources to its advisory committee process. In relation to the FDA's total budget, the incremental costs of modifying the advisory committee system appear relatively modest when compared to the potential benefits that can be expected to accrue to the agency.

Appendix B

Glossary

Abbreviated New Drug Application, or ANDA: A simplified submission permitted for a duplicate of an already approved drug. ANDAs are for products with the same or very closely related active ingredients, dosage form, strength, administration route, use, and labeling as a product that has already been shown to be safe and effective. An ANDA includes all the information on chemistry and manufacturing controls found in a new drug application (NDA), but does not have to include data from studies in animals and humans. It must, however, contain evidence that the duplicate drug is bioequivalent (see "Bioequivalence") to the previously approved drug.

Action Letter: An official communication from the FDA to an NDA sponsor that informs it of a decision by the agency. An *approval letter* allows commercial marketing of the product. An *approvable letter* lists minor issues to be resolved before approval can be given (see "Conditional Approval"). A *not approvable letter* describes important deficiencies that preclude approval unless corrected.

Advisory Committee: A panel of outside experts convened periodically to advise the FDA on safety and efficacy issues about drugs and other FDA-regulated products. The FDA is not bound to follow committee recommendations, but its decisions usually parallel the recommendations of its advisory committees.

Amendment to an NDA: Submitted to change or add information to a not yet approved NDA or a supplement.

Approval: The FDA approves the application without conditions, or if the company agrees to the specified conditions, and the company may begin to market the technology upon receipt of the order.

Bench Testing: Testing of a device against specifications in a simulated environment that does not include the living body of a human or animal. Also known as in vitro device readiness testing.

Bioavailability: The rate and extent to which a drug is absorbed or is otherwise available to the treatment site in the body.

Bioequivalence: The scientific basis on which generic and brand-name drugs are compared. To be considered bioequivalent, the bioavailability of two products must not differ significantly when the two products are given in studies at the same dosage under similar conditions. Some drugs, however, are intended to have a different absorption rate. The FDA may consider a product bioequivalent to a second product with a different rate of absorption if the difference is noted in the labeling and does not affect the drug's safety or effectiveness or change the drug's effects in any medically significant way.

Class I: An FDA classification of devices for which the general controls of the Food, Drug, and Cosmetic Act are sufficient to provide a reasonable assurance of safety and effectiveness. Approximately 30 percent of devices are in Class I.

Class II: Devices for which Class I controls alone are not sufficient but for which these controls plus special requirements win provide reasonable assurance of safety and effectiveness. Approximately 60 percent of devices are in Class II.

Class III: A premarket approval class for devices that cannot be placed in either Class I or Class II. A device in this class has at least one of the following characteristics: it is purported for use in supporting or sustaining human life or for a use that is of substantial importance in preventing the impairment of human health; it presents a potentially unreasonable risk of illness or injury; or it is a transitional device. Approximately 10 percent of devices are in Class III.

Clinical Studies: Clinical, or human, studies aim to distinguish a drug's effect from other influences—for example, a spontaneous change in disease progression or in the effect of a placebo (an inactive substance that looks like the test drug). Such studies conducted in this country must be under an approved IND (see "Investigational New Drug Application"), under the guidance of an institutional review board, in accord with FDA rules on human studies, and with the informed consent of participants.

CNDA: Computerized NDA; see "NDA."

Conditional Approval: The FDA sends an approvable letter (see "Action Letter" and "Approval"), citing specific conditions to which the company is asked to agree. This means that the FDA believes there is reasonable assurance of safety and effectiveness, but that certain conditions must be imposed on the company.

Diffusion: The process by which use of a technological innovation in a given social system spreads over a period of time. (See "Technological Innovation.")

Drug Substance: The active ingredient intended to diagnose, treat, cure, or prevent disease or affect the structure or function of the body, excluding other inactive substances used in the drug product.

Effectiveness: In health care policy and clinical care, "effectiveness" usually refers to the performance and evaluation of a health care technology in general clinical use. "Efficacy," by contrast, is used to denote the use and evaluation of a health care technology under highly controlled conditions by unusually qualified practitioners. Unfortunately, in various pieces of legislation pertaining to the FDA, effectiveness is used to refer to the controlled, highly evaluative use usually associated with the evaluation of efficacy. Because the definitions of effectiveness that are set out in law are contrary to the usual meaning of the word, when used by the FDA "effectiveness" often refers to what can more precisely—or consistently—be called efficacy.

Efficacy: See "Effectiveness."

Enforcement: Before a product is marketed, enforcement is the monitoring of clinical investigators and product sponsors. Once a product is on the market, enforcement also includes the inspection of products and manufacturers.

Investigational New Drug Application, or IND: An application that a drug sponsor must submit to the FDA before beginning tests of a new drug on humans. The IND contains the plan for the study and is supposed to give a complete picture of the drug, including its structural formula, animal test results, and manufacturing information.

In vitro bench testing: See "Bench Testing."

In vivo testing:	Testing in the living body of a plant or animal.
New Drug:	A drug first investigated or proposed for marketing after 1938, when the Federal Food, Drug, and Cosmetic Act was passed. This means that the drug was not generally recognized as safe and effective before that date.
New Drug Application, or NDA:	An application requesting FDA approval to market a new drug for human use in interstate commerce. The application must contain, among other things, data from clinical studies needed for FDA review from specific technical viewpoints, including chemistry, pharmacology, medical, biopharmaceutics, statistics, and—foranti-infectives—microbiology.
Pharmacology:	The science that deals with the effect of drugs on living organisms.
Post-Marketing Surveillance:	FDA's ongoing safety monitoring of marketed drugs.
Pre-Clinical Studies:	Studies that test a drug on animals and other nonhuman test systems. They must comply with the FDA's good laboratory practices. Data about a drug's activities and effects in animals help establish boundaries for safe use of the drug in subsequent human testing (clinical studies). Also, because animals have a much shorter life span than humans, valuable information can be gained about a drug's possible toxic effects over an animal's life-cycle and on offspring.
Pre-Market Approval:	The device manufacturer must provide reasonable assurance of safety and effectiveness under the conditions of intended use. Under the 1976 Medical Device Amendments, the FDA had to submit all pre-marketing approval applications to an advisory committee for a recommendation on the decision. The Safe Medical Devices Act of 1990, however, allows the FDA discretion in deciding which applications to submit to an advisory committee.
Pre-Market Notification (510 (k)):	The manufacturer presents evidence that its device is substantially equivalent to an earlier, approved device. Approximately 5,000 to 6,000 510(k)s are received in a year, and about 90 percent of devices thus submitted are judged to be substantially equivalent. If the device is not substantially equivalent, it is placed in Class III (which requires pre-market approval) and cannot be marketed until a pre-market

approval application is approved or the device is reclassified. Although advisory committee members may be consulted, there is no legal requirement for their involvement.

Prevalence: The number of persons in a population that are affected with a particular disease at a given time.

Raw Data: Researcher's records of patients, such as patient charts, hospital records, X-rays, and attending physician's notes. They may or may not accompany an NDA, but must be kept in the researcher's file. The FDA may request their submission.

Review Clock: The time frame of 180 days allowed the FDA to review NDAs. The "clock" starts on the date the NDA is received and stops on the date a final action (see "Action Letter" entry) is taken. The FDA may extend the time if significant changes are made to a pending NDA. From the time an NDA is submitted to when it is approved usually is more that 180 days, for any number of reasons—notably, time-consuming amendments to the NDA or a shortage of trained FDA reviewers.

Safety Update Reports: Reports that an NDA sponsor must submit to the FDA about any new safety information that may affect the draft labeling statements about contraindications, warnings, precautions, and adverse reactions. Safety update reports are required four months after the application is submitted, after the applicant receives an approvable letter, and at other times upon the FDA's request.

Supplement: A marketing application submitted for changes in a product that already has an approved NDA The FDA must approve all important NDA changes (in packaging or ingredients, for instance) to ensure the conditions originally set for the product are not adversely affected.

Surveillance: The monitoring of adverse reactions and product defects in drugs, biologics, devices, and foods.

Technological innovation: The process of creating, inventing, or adapting a technology which for a given sector of society, organization, or user. A technology can be a drug, device, clinical procedure, clinical system (e.g, hospital or intensive care unit).