TASK ORDER NO. 14
CONTRACT NO. 223-03-8500

Final

MEASURING CONFLICT OF INTEREST AND EXPERTISE ON FDA ADVISORY COMMITTEES

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October 26, 2007

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EXECUTIVE SUMMARY

Under contract to the US Food and Drug Administration, Eastern Research Group, Inc. (ERG) assessed the relationship between expertise and financial conflicts of interest of FDA advisory committee members. This report describes the results of ERG's analysis based on a sample of advisory committee meetings from recent fiscal years.

Our main finding is that standing advisory committee members with higher overall measures of expertise were more likely than other standing advisory committee members to have been granted waivers for financial conflicts of interest.

We also found that potential alternative experts can be initially identified, but that some of these individuals may not otherwise be appropriate or available to serve as advisory committee members. In particular, many alternative experts would also require waivers. Overall we judge the ability to create alternative conflict-free advisory panels to be speculative. If possible, it would represent an uncertain and potentially substantial additional burden on the cost and the timeliness of advisory committee operations. Further, FDA might not always be able to match the specialized expertise of some existing advisory committees.

Currently, FDA advisory committee members who have financial relationships with regulated industry may be granted waivers for participation in meetings. Waivers are often granted because the need for the member's specific expertise outweighs the potential for a conflict of interest. Some people believe that conflicts of interest lead to inherent biases in the recommendations made to FDA regarding important issues of public health and safety. Further, they suggest that other qualified specialists, without conflicts, are available to serve on committees.

ERG measured the relationship between financial conflicts of interest and expertise among standing advisory committee members. The study uses a sample of 16 advisory committee meetings and 124 standing advisory committee members. For each member, ERG collected total numbers of publications, years of experience, and an "H-index." The H-index is a tool used in citation analysis that attempts to measure scientific productivity by tallying an author's publications, h, with at least h citations each. These variables are assumed to be simple, reasonable, and generally comparable among experts in the sample.

Combining the expertise variables, ERG generated an overall measure of expertise: a composite expertise index. The mean expertise index of members with waivers (0.40) was higher than the respective mean of those without waivers (0.31). Thus, members in the sample with waivers tend to have higher

levels of general expertise than members without waivers, based on the overall expertise measures defined in this study.

Using conflict of interest data provided by FDA, ERG also calculated the total dollar value of conflict associated with each waiver granted to a member in the sample. The median total dollar value of financial interest for members with waivers was $14,500. However, near-zero rank correlation coefficients suggest that there is no relationship between measures of expertise and the total dollar value of the financial conflict.

Finally, ERG assessed the possibility of identifying alternative candidates, with fewer or no conflicts of interest, to replace a selection of 17 members who were granted waivers for the meetings within our sample. Using the Thompson Web of Science® database, Entrez PubMed, and other Internet tools, ERG identified 70 potential alternative candidates whose expertise index met or exceeded the mean expertise index of current members with waivers. Next, using a literature search for financial conflict disclosures in published journal articles, FDA and ERG assessed how likely the potential candidates would be to also require waivers for participation on advisory committees. This analysis suggests that alternative candidates might exist, but that many would require waivers. ERG did not contact these 70 potential alternatives to determine their willingness or interest in participating in the advisory committee process. We conclude that the ability to create a conflict-free panel is speculative, and that, even if possible, recruiting and screening costs would be much higher than current expenditures. Furthermore, the additional time required to screen candidates could significantly delay FDA decisions on major public health issues.

The reader should note important limitations on our ability to precisely measure expertise, particularly across scientific disciplines, and at the level of specific topics within disciplines. For example, rates of publication, whether in peer-reviewed journals or other formats, may be inherently larger in certain disciplines than others, thus making comparisons across disciplines by total number of publications problematic. These limitations should be kept in mind in assessing our comparisons about the relative levels of expertise among FDA advisory committee members.

1. INTRODUCTION

The mission of the U.S. Food and Drug Administration (FDA) is to protect the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, and products that emit radiation. FDA regulates the safety and efficacy of more than 150,000 marketed drugs and medical devices, oversees the distribution of thousands of investigational new drugs, and helps assure the safety of a wide range of food products and dietary supplements. FDA established advisory committees to provide "independent expertise and technical assistance related to the development and evaluation of products regulated by FDA" (FDA Handbook, 1994).[1]

Advisory committees are called upon to "lend credibility to the product review process" and to "provide a forum for public discussion of certain controversial issues" (FDA Handbook, 1994). For specific products, advisory committees consider the available evidence and provide scientific and medical advice on safety, efficacy, and appropriate use. Committees might also be relied upon to participate in the agency's decision-making process on broader regulatory and scientific issues. Advisory committee meetings can occur during any stage of a product's review process or, if necessary, as post-marketing issues arise. Committee recommendations remain advisory in nature, as all final decisions on both policy and technical matters are made by FDA.

Over the years, there has been increasing scrutiny of the financial conflicts of interest of FDA advisory committee members (Glodé, 2002; Steinbrook, 2005; Lurie, 2006; Kondro, 2006; Zuckerman, 2006). A conflict of interest exists when a person has influence on official decisions where the outcomes of those decisions might affect his or her private interests. A conflict of interest is a condition rather than a behavior; its existence does not imply that a person will act in a biased manner (Smith, 2006). Nevertheless, some people are concerned with advisory committee members' financial, professional, or personal stakes in the guidance that advisory committees render to FDA regarding public health and safety.

Under the current system, FDA advisory committee members with financial conflicts of interest can be granted waivers for participation. This system is based on the rationale that the leading experts on an issue, technology, or product often have some connection to regulated industry. Some people suggest that highly qualified experts without conflicts of interest are available to serve on advisory committees.

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[1] See Glodé, 2002 for a historical overview of the FDA Advisory Committee system.

They believe that waivers are unnecessary and might lead to biases in advisory committee recommendations.

In general, the discussion regarding the appropriateness of waivers has focused on conflicts of interest at particular advisory committee meetings, such as those for Vioxx, Levaquin, Provigil, and Tysabri. (See, for example, Angell, 2005; Barlas, 2006; Cauchon, 2000; Gribbin, 2001; Harris, 2006; Henderson, 2006; and Saul, 2005.) This study introduces systematic measures regarding the relationship between conflicts of interest and expertise among advisory committee members through its use of the composite expertise index.

This study has four objectives:

1. To measure conflicts of interest for a sample of standing advisory committee members who participated in an advisory committee meeting and summarize the type and value of reported financial conflicts of interest where waivers were granted;
2. To measure overall expertise for a sample of standing advisory committee members who participated in an advisory committee meeting;
3. To estimate the relationship between overall expertise and conflict of interest for standing advisory committee members who participated in an advisory committee meeting; and
4. To create hypothetical meeting rosters of standing advisory committee members for a sample of meetings by identifying individuals that would not require a waiver but match the overall expertise of a standing committee member at an actual advisory committee meeting.

Section 2 of this report provides an overview of FDA advisory committees and how expertise and conflicts of interest are defined. Section 3 of this report describes the study methodology, including how the sample was chosen. Section 4 outlines our use of FDA financial conflict of interest data to evaluate and measure the conflicts for the standing advisory committee members in our sample. Section 5 describes our process for measuring overall expertise among scientific experts. Based on various measures of expertise, as well as a composite index, we provide an analysis of expertise among our sample, including a comparison between those members with waivers for conflicts of interest and those without waivers. Section 6 addresses the correlations between overall expertise and conflicts within the sample of advisory committee members. Finally, Section 7 focuses on the feasibility of creating hypothetical advisory committee meetings such that participants with waivers are hypothetically replaced in order to create a meeting roster where no one requires a waiver.

1.1 BACKGROUND ON FDA ADVISORY COMMITTEES AND CONFLICTS OF INTEREST

Most advisory committee members are expert scientists and esteemed clinicians.[2] Such highly-expert individuals are also often in high demand as consultants to regulated industry, as principal investigators for clinical trials or as speakers' bureau members. They might purchase stock or make investments in various companies. Academic and institutional research also increasingly relies on industry sources for funding (Bekelman, 2003; Glodé, 2002). This situation, whereby the same experts are in demand by both the federal government and regulated industry, has been described by McComas, et al. as the "shared pool dilemma" (2005).

To ensure the transparency and impartiality of the committee process, FDA advisory committees are governed both by the Federal Advisory Committee Act and Agency-established guidelines. Voting and non-voting committee members (except industry representatives) are designated as special government employees (SGEs). SGEs are subject to regulations governing Federal employees. Specifically, 18 U.S.C. 208 prevents committee members from participating in matters where they might have a disqualifying financial interest. FDA ordinarily requests that prospective committee members disclose potential financial conflicts to the agency before they are appointed as committee members and complete more formal disclosures prior to participating in each meeting.

In advance of every meeting, SGEs are required to complete FDA Form 3410: Confidential Financial Disclosure Report for Special Government Employees. On this form, participants must disclose current and past financial interests relating to the products, firms, and issues that pertain to the meeting topic (as described by FDA in a cover memorandum to the SGE).[3] Based on these disclosures, FDA addresses the "shared pool dilemma" by granting waivers to advisory committee meeting participants with disqualifying financial interests as required by 18 U.S.C. Sec. 208(b) (see Table 1-1). Waivers can be full, granting the member voting privileges to fully participate in a meeting, or limited, granting participation in discussions but excluding the individual from voting. Table 1-1 describes the categories under which waivers are granted to advisory committee members.

Some people suggest that waivers should not be permitted, as the presence of a conflict renders a committee member unable to provide an expert opinion in an unbiased and autonomous manner. As a condition rather than a behavior, however, the presence of a conflict does not necessarily imply that a member will act in a biased manner (McComas, et al., 2005). FDA is concerned that, by excluding

[2] Advisory committees also include industry and consumer representatives. Meetings of advisory committees also regularly include additional experts as temporary voting or non-voting members.
[3] Intellectual conflicts are difficult to quantify or analyze and are not the subject of this study.

members who require waivers, they will lose the most qualified experts, and thus diminish the quality of scientific advice regarding important public health decisions.

Table 1-1: Waivers Available for Participants of FDA Advisory Committee Meetings

U.S. Regulation	Description
18 U.S.C. § 208(b)(1)	Waiver can be granted if the size of the financial interest is fully disclosed and the agency determines 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 officer or employee."
18 U.S.C. § 208(b)(2)	Waiver can be granted if the financial interest is "too remote or too inconsequential to affect the integrity of the services of the Government officer."
18 U.S.C. § 208(b)(3)	Waiver can be granted if "the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved."
21 U.S.C. § 355(n)(4)[4]	Waiver could be granted if the member (or his/her immediate family) could gain financially from a decision, but his/her participation was necessary to provide the committee essential expertise. No waiver was allowed when the member's own scientific work is involved. Member might have also needed an additional Section 208 waiver.

Source: United States Code, 2000 Edition, Supplement 4.
Note: Section 355(n)(4) applied only to individuals working on certain panels concerning a clinical investigation of, or approval for marketing of, a drug (including a biological product).

[4] On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act of 2007, which included new conflict of interest provisions applicable to FDA advisory committees and repealed the conflict of interest provisions in 21 U.S.C. 355(n)(4). *See* Pub. L. No. 110-85, § 701. Because these provisions became effective October 1, 2007, and were not applicable during this study, we do not discuss the details of the legislation in this report.

2. OVERVIEW OF FDA ADVISORY COMMITTEES

The Federal Advisory Committee Act (Pub. L. 92-463) and the Food and Drug Administration Modernization Act of 1997 (21 U.S.C. 355(n)(1)) regulate the establishment of FDA advisory committees. Some FDA advisory committees are congressionally mandated, but many are formed and dissolved at the discretion of the Department of Health and Human Services.

There are currently 31 FDA advisory committees, although one committee has 18 sub-panels serving as independent advisory bodies. These 48 advisory bodies provide advice on topic areas for the FDA Office of the Commissioner and each of the following six FDA centers:

- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Drug Evaluation and Research (CDER)
- Center for Veterinary Medicine (CVM)
- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)
- National Center for Toxicological Research (NCTR).

To provide inclusive representation, there are four different FDA advisory committee membership types: academicians/practitioners, consumers, patients, and industry professionals. Committees have on average ten standing members, who serve staggered four-year terms. Although members can serve up to eight years within a twelve-year time period, they may not serve consecutive terms.

Standing committee members are selected from qualified candidates with relevant professional, scientific, or academic experience. Like their academic and clinical colleagues, consumer representatives are typically voting members and therefore are required to be "technically and scientifically qualified" to analyze research design and scientific data (FDA Handbook, 1994).[5] Industry representatives are non-voting members. In addition to standing members, temporary voting members may be appointed to attend a single committee meeting when a quorum is needed or additional expertise is required. Temporary members may or may not be granted voting privileges.

[5] Consumer representatives are not voting members on advisory committees for the Center for Devices and Radiological Health.

FDA posts impending vacancies for advisory committee positions in a Federal Register notice, as well as on an internet website which shows current vacancies on all of its committees. FDA advisory committee staff members may also recruit members by networking at large events, such as national meetings of relevant professional organizations (FDA Handbook, 1994).

According to the Policy and Guidance Handbook for FDA Advisory Committees, all potential candidates must meet certain general criteria. Specifically, they are required to:

- Have the background, education and experience commensurate with the purposes and objectives of the individual committee and the advice they are expected to render. Scientific and technical competence is critical.
- Be at least 21 years of age.
- Preferably be a United States citizen.

In addition to the basic criteria, candidates are carefully screened to assure that they possess expertise relevant to the particular committee or subject matter on which their advice will be sought.

FDA officials confirm that selecting advisory committee members is not an easy task. In many cases, recommendations for members are accepted from FDA's internal product review division and existing committee members. Resumes or curriculum vitae of candidates are reviewed for attributes that are suggestive of highly qualified individuals, such as professional titles held, years of experience, board certifications, specialties, and high numbers of publications. Letters of recommendation are also acquired from outside sources. In some cases, candidates are invited to serve as temporary members of advisory committees to ensure a good fit before they are invited to serve as standing members (Wood, 2006).

Finding a balance for advisory committee membership is crucial, in terms of expertise, specialty, and opinion, as well as race/ethnicity, gender, and geography. Such balance is important for impartiality and transparency; it is also specifically mandated under the Federal Advisory Committee Act. FDA also stresses the importance of finding members who are well respected in their careers so that the reputation of the individual would be able to carry the weight of any decision that may be made (Freas and Dapolito, 2006).

2.1 FDA STANDARDS FOR CONFLICT OF INTEREST

FDA typically screens potential advisory committee members who are SGEs or regular government employees for substantial conflicts of interest before being appointed. Before each advisory committee meeting, such members are also asked to complete FDA Form 3410 in order to disclose to the agency information regarding potential financial conflicts of interest in relation to the meeting topic (for

either particular matters involving specific parties or particular matters of general applicability). FDA requires information on financial interests related to:

- Stocks and investments
- Primary employment
- Consulting or advising
- Contracts/Grants/Cooperative Research and Development Agreements (CRADAs)
- Patents/Royalties/Trademarks
- Serving as Expert Witness
- Teaching/Speaking/Writing

Advisory committee management reviews the disclosures and makes determinations regarding member recusals or requests for waivers, which are reviewed by the FDA Ethics Staff. These are then approved or denied by the FDA Commissioner or his/her designated official. FDA has developed guidance for determining the appropriate course of action when a special government employee has a potential conflict of interest. The current guidance document, known as the FDA Waiver Criteria 2000 Document,[6] has been commended as a model for use by other Executive Branch agencies.

Factors that are considered in the decision to grant a waiver include the following:

- Is the conflict with a sponsor of the drug for which recommendations will be given or with a company producing a competing product (i.e. a competitor)?
- Is the conflict a direct interest (i.e. stock or consulting fees) or imputed financial interest of an employer/affiliated organization?
- Is the topic of the meeting product specific or does it involve an entire class of products?
- Is the specific expertise of the individual otherwise unavailable?
- Is the issue/product in question widely studied such that other qualified participants would likely have similar conflicts?
- Is there a benefit to granting a limited waiver in place of a full waiver or recusal?

Due to their complicated nature, FDA evaluates each potential conflict of interest in the context of all mitigating factors. Nonetheless, there are often common courses of action for different types of

[6] Available at http://www.fda.gov/oc/advisory/conflictofinterest/intro.html. (Accessed: February 7, 2007)

conflicts. FDA Waiver Criteria 2000 Document tables categorize conflicts by involvement level and identify circumstances in which it is most likely that a waiver will be granted.[7]

In 2002, FDA issued a draft guidance on the public disclosure of conflicts of interest.[8] In order to promote transparency, the committee's executive secretary reads a statement at the beginning of each meeting, indicating the names of members granted waivers and the type of waiver they have been granted.

2.2 DEFINING EXPERTISE

An expert is "one with the special skill or knowledge representing mastery of a particular subject" or a person "having, involving, or displaying special skill or knowledge derived from training or experience" (Merriam-Webster, 2007). Nevertheless, attempting to objectively measure expertise, or the proficiency of an expert, is inherently difficult and controversial. In their paper, *Empirical Assessment of Expertise*, Weiss and Shanteau (2003) note that there are "well-established procedures for assessing expertise when gold standards exist" to gauge outcomes. However, "experts are needed precisely in those domains where there are not correct answers" (Weiss and Shanteau, 2003). Therefore, evaluations, such as those provided by FDA advisory committees, require professional judgment.

One would expect there to be a relationship between experience and expertise. Expert status is often typically achieved after "long, established careers, which can include tenure at a respected university, an impressive publication record, a successful track record of obtaining extramural funding, and other public service or private consulting activities" as well as "working in their respective disciplines for many years" (McComas, et al., 2005). Faculty and tenure decisions, which are often a judgment of expertise, are typically based on exemplary past performance, i.e. experience in teaching, research, and service. Experience is also often used as a benchmark for determining the credibility of expert witnesses. Other criteria used for establishing one as an expert include: education, professional certification and associations, licensing, and credibility with peers.

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[7] In March 2007, FDA issued a draft guidance document for the public, FDA Advisory Committee members, and FDA staff entitled "Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees" (http://www.fda.gov/oc/advisory/waiver/COIguidedft.html). This draft guidance document, when finalized, would establish a new FDA policy for reviewing conflicts of interest and determining who may participate in FDA advisory committee meetings. FDA is in the process of evaluating the draft guidance in light of new statutory provisions addressing conflicts of interest and the public comments it has received.

[8] Food and Drug Administration, Draft Guidance on Disclosure of Conflicts of Interest for Special Government Employees Participating in FDA Product Specific Advisory Committees, available at http://www.fda.gov/oc/guidance/advisorycommittee.html (Accessed: February 7, 2007).

3. STUDY METHODOLOGY

For the purposes of measuring expertise and conflict of interest, a sample of advisory committee meetings was selected. The sample was chosen from FDA advisory committee meetings held between December 2005 and October 2006. Working in reverse chronological order, we selected a set of meetings for inclusion in the sample such that the following conditions were met:

1. Stratification between Centers: Approximately 50 percent of the sample consisted of CDER meetings, 30 percent of CDRH meetings, and 20 percent of CBER meetings. We selected no meetings from CVM, CFSAN, NCTR, or the Office of the Commissioner because those committees meet infrequently.
2. During the meeting, a formal vote regarding safety and efficacy was taken. Meetings involving particular matters of general applicability were excluded from the sample.
3. At least one waiver was granted to a standing member of the committee.
4. Curriculum vitae for standing members are available online or from FDA.
5. The final sample contains at least 100 members and about 25 percent of those members have waivers.

In sum, 16 advisory committee meetings (representing 18 individual sessions)[9] were identified between December 14, 2005 and October 4, 2006. Table 3-1 shows the selected committees, meetings, sessions, dates and topics. A total of 260 participants attended the selected meetings and sessions. This count does not include FDA officials. Table 3-2 summarizes the data on meeting participants.

Some participants attended more than one meeting in our sample or attended multiple sessions of the same meeting.[9] Of the 211 individual meeting participants, 45 (21%) received at least one waiver. The majority of waivers granted (70%) were for standing committee members. The other 18 waivers were granted to temporary voting members (10), consumer representatives (4), and patient representatives (4).

Industry representatives, temporary voting members, patient representatives, and consumer representatives who were not standing members of a committee were excluded from our analysis. Industry representatives are non-voting members and do not receive waivers for conflicts of interest. For the others, we lacked the appropriate data to characterize their overall level of expertise in the same manner as their academic or clinical colleagues. For example, patient and consumer representatives do not typically publish many peer-reviewed studies or generate other quantifiable measures of expertise. Temporary voting members (sometimes referred to as consultants) are invited to participate in meetings

[9] Advisory committee meetings are often divided into morning and afternoon sessions, with different topics for discussion and voting at each session.

where they can provide specialized topic-relevant expertise. Therefore, the criteria by which their expertise is deemed essential might be different than that for standing advisory committee members. Given the inconsistencies that might result from this difference, ERG conducted an analysis of standing advisory committee members only. Since the report focuses on overall expertise rather than topic-specific expertise, the exclusion of temporary voting members is not significant.

Table 3-1: Selected Study Sample of FDA Advisory Committee Meetings and Sessions

Center	Panel	Meeting Date	Meeting/Session Topic
CBER	Vaccines and Related Biological Products	12/14/2005	RotaTeq
CBER	Blood Products Advisory Committee	3/9/2006	Rapid tests
CDER	Joint meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee	1/23/2006	Tetrahydrolipstatin (Orlistat, GlaxoSmithKline)
CDER	Joint meeting of the Nonprescription Drugs Advisory Committee and Pulmonary-Allergy Drugs Advisory Committee	1/24/2006	OTC use of epinephrine-metered dose inhalers (MDIs)
CDER	Peripheral and Central Nervous Drugs	3/7/2006	Natalizumab injection (Tysabri, Biogen Idec and Elan Pharmaceuticals)
CDER	Psychopharmacologic Drugs Advisory Committee	3/23/2006	Modafinil tablets (Provigil, Cephalon)
CDER	Peripheral and Central Nervous	5/17/2006	Rivastigmine tartarte (Exelon, Novartis)
CDER	Oncologic Drugs Advisory Committee	6/2/2006	Dasatinib (Sprycel, Bristol Myers Squibb)
CDER	Oncologic Drugs Advisory Committee [a]	9/6/2006	Dalteparin sodium injection (Fragmin, Pfizer)
CDER	Oncologic Drugs Advisory Committee [a]	9/6/2006	Oblimersen sodium (Genasense, Genta)
CDER	Oncologic Drugs Advisory Committee [a]	9/7/2006	Paclitaxel protein-bound particles for injectable suspension (albumin-bound) (Abraxane, Abraxis BioScience)
CDER	Anti-Infective Drugs Advisory Committee	9/12/2006	Gemifloxacin mesylate (Factive, LG Life Sciences)
CDER	Cardiovascular and Renal Drugs Advisory Committee	9/21/2006	Aprotinin injection (Trasylol, Bayer Pharmaceuticals)
CDER	Pharmaceutical Science Advisory Committee	10/4/2006	Levothyroxine sodium drug products
CDRH	Orthopedic and Rehabilitation Devices Panel	6/2/2006	Non-invasive bone growth stimulators
CDRH	Ophthalmic Devices Panel	7/14/2006	Implantable miniature telescope (IMT)
CDRH	Orthopedic and Rehabilitation Devices Panel	9/19/2006	Cervical disc prosthesis (Medtronic Sofamor Danek)
CDRH	General and Plastic Surgery Devices Panel	9/24/2006	Injectable calcium hydroxylapetite implant (Radiesse, BioForm Medical)

Note: CBER: Center for Biologics Evaluation and Research; CDER: Center for Drug Evaluation and Research; CDRH: Center for Devices and Radiological Health.

[a)] The Oncologic Drugs Advisory Committee meeting that took place on September 6 and 7, 2006 consisted of three separate sessions.

Our final sample consists of 124 individual standing advisory committee members, including standing member consumer representatives. Of these 124 individuals, 32 (26%) had waivers for participation in at least one meeting or session. Multiple waivers were granted to one-quarter of those participants with waivers.

Table 3-2: Summary of Participants and Waivers at Sample Meetings

Participant Type	Total Participants at Meetings (individuals) [a]	# of Waivers Granted to Participants (individuals) [a]	Percent of Participants with Waivers	Percent of Individuals with Waivers	Percent of Total Waivers Granted
Standing members	144 (113)	42 (30)	29%	27%	70%
Temporary voting members	86 (74)	10 (9)	12%	12%	16.70%
Consumer representatives	14 (11)	4 (2)	29%	18%	6.70%
Industry representatives	9 (6)	NA	NA	NA	NA
Patient representatives	7 (7)	4 (4)	57%	57%	6.70%
TOTALS	**260 (211)**	**60 (45)**	**23%**	**21%**	**100%**

Source: Data compiled by ERG.

Note: Industry representatives are non-voting and were not included in the sample. Patient representatives and temporary voting members were not included in the analysis for lack of comparable data.

[a)] The number of participants is greater than the number of individuals (in parentheses), as some individuals attended more than one meeting or multiple sessions of the same meeting.

4. MEASURING CONFLICT OF INTEREST

ERG provided to FDA the names of the 32 standing advisory committee members within our sample who were granted waivers for participation in a meeting. FDA supplied us with a database of information regarding the nature and magnitude of conflicts of interest for each waiver granted.[10] The total number of waivers granted to these 32 members was 46. We utilized this data to evaluate their conflicts of interest.

FDA provided data on the type of waiver granted (as described in Table 1-1). The majority of waivers (85%) were granted under 18 U.S.C. § 208(b)(3). These waivers may be granted when the potential for conflict of interest is outweighed by the need for the individual's services. The factors that FDA considers in making this determination (described in greater detail in section 2.1 of this report) include the type and magnitude of the financial interest and the difficulty in locating a similarly qualified individual. Six members were granted waivers to permit voting participation under 21 U.S.C. § 355(n)(4).[11] These waivers were granted if the committee member or a member of his/her immediate family could have gained financially from the committee's decision, but the member's participation afforded the committee essential expertise. Three members were granted both types of waivers for attendance at the same meeting.

ERG evaluated the magnitude of conflict by the following categories of assets: stocks and investments; primary employment; consulting or advising; contracts, grants, cooperative research and development agreements (CRADAs); patents, royalties, and trademarks; serving as expert witness; and teaching/speaking/writing. Within each category, conflicts are also classified according to conflict type: those with the sponsor of the relevant product and those with any company who manufactures or intends to develop a competing product (i.e., competitors).

Table 4-1 provides summary statistics for the financial conflicts of interest within our sample. The data describe the value of the assets that represent conflicts of interest. Columns and rows do not sum to the total values because some individuals had conflicts with both a product sponsor and a competitor. The mean dollar value of conflict per waiver is $25,787 and the median dollar value of conflict is $14,500.

No members in the sample received waivers for financial conflicts in the categories of stock options, patents, employment, or expert witness fees. In addition, two members received waivers for

[10] Allan Begosh of FDA created and managed the FDA database of advisory committee member conflicts of interest.
[11] See footnote 4.

which no dollar amount of conflict was established. One member received a waiver for negotiating employment with an organization that has an interest in the meeting, and the other member received a waiver for membership in an undisclosed organization.

Table 4-1: Summary Statistics for Conflicts of Interest in a Sample of Members, by Category

	Conflicts with Sponsors	Conflicts with Competitors	Total Conflicts [a]
Stock	**n=3**	**n=13**	**n=15**
mean	$534.02	$11,876.76	$12,410.78
median	$0	$0	$0
maximum	$19,013	$96,893	$102,922
Consulting Fees	**n=6**	**n=19**	**n=21**
mean	$1266.85	$4,214.63	$5,481.48
median	$0	$0	$0
maximum	$30,000	$36,100	$36,100
Speaking Fees	**n=1**	**n=7**	**n=7**
mean	$365.22	$1,792.46	$2,157.67
median	$0	$0	$0
maximum	$16,800	$48,000	$48,000
Contracts, Grants, CRADAs	**n=2**	**n=4**	**n=6**
mean	$998.07	$4,565.22	$5,563.28
median	$0	$0	$0
maximum	$23,160	$100,000	$100,000
Other	**n=0**	**n=2**	**n=2**
mean	$0	$173.91	$173.91
median	$0	$0	$0
maximum	$0	$7,500	$7,500
Stock Options	**n=0**	**n=0**	**n=0**
Patents	**n=0**	**n=0**	**n=0**
Employment	**n=0**	**n=0**	**n=0**
Expert Witness Fees	**n=0**	**n=0**	**n=0**
Total Conflicts	**n=12**	**n=38**	**n=44**
mean	**$3,164.15**	**$22,622.97**	**$25,787.13**
median	**$0**	**$10,000**	**$14,500**
maximum	**$30,000**	**$100,000**	**$102,922**

Source: Data from FDA, 2007, compiled by ERG.
Note: This table does not include the two advisory committee members who were granted waivers but had no dollar value of conflict established.
a) Conflicts with sponsors and conflicts with competitors do not sum to total conflicts because some members had conflicts with both sponsors and competitors.

Overall, there were more conflicts with competitors than with sponsors of the products or issues on the meeting agendas. Of the twelve members who had conflicts with a product sponsor, 50 percent also had conflicts with a product competitor. On average, the conflicts with competitors were also of higher financial value. Table 4-2 provides an overview of the nature of conflicts with both product sponsors and competitors.

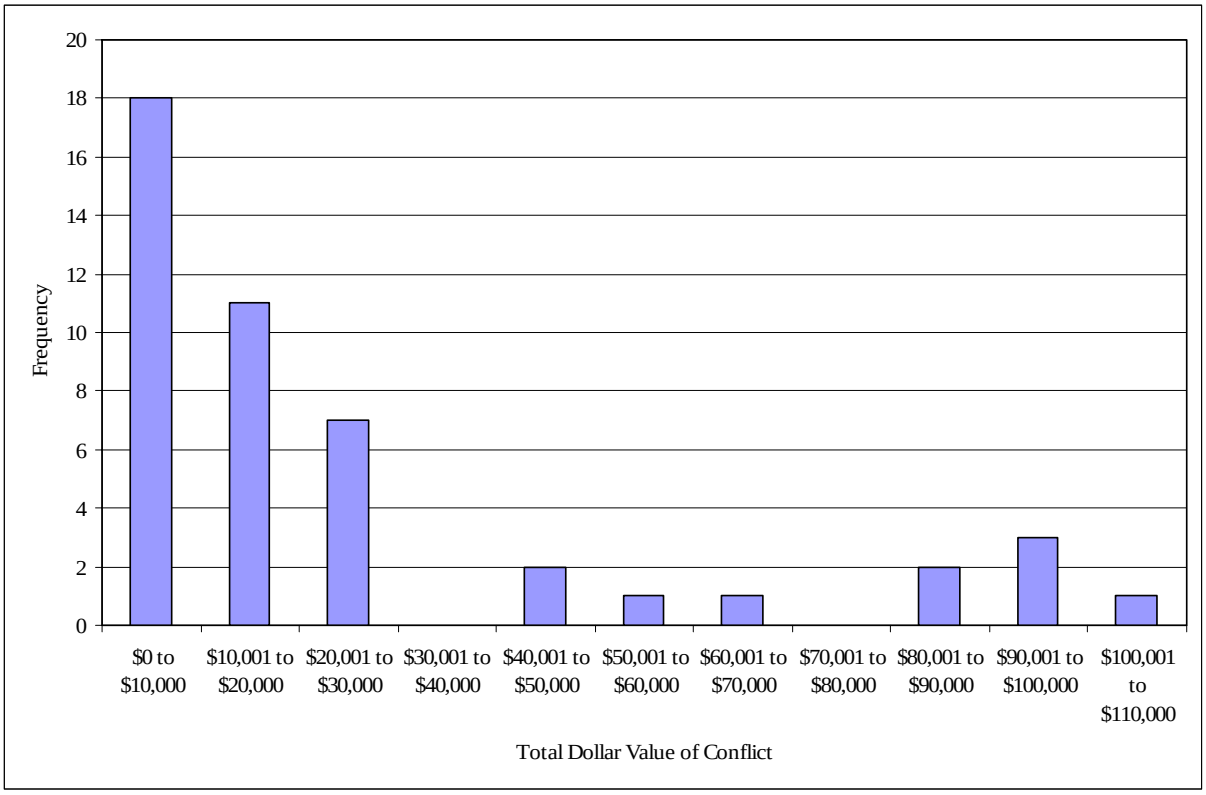
Table 4-2: Conflicts Among Sample of Members, by Type

	Sponsor	Competitor
Number of Conflicts	12	45
Ongoing Relationships	12	6
Past Relationships	0	Not listed
Direct Conflict	8	35
Imputed Conflict	4	5

Source: Data from FDA, 2007, compiled by ERG.
Note: Individual categories do not sum to the total number of conflicts because complete information was unavailable.

To generate overall measures of conflict, we calculated the total dollar value of conflicts for each record in the database by summing the amounts for each individual type of conflict (e.g., stocks, consulting, etc.). Figure 4-1 shows the frequency distribution for total dollar value of all conflicts for each waiver granted within the sample. Seventeen percent of financial conflicts had a total dollar value above $50,000; thirty-nine percent of conflicts were valued under $10,001.

Figure 4-1: Frequency Distribution of Total Dollar Value of Conflicts



Source: Data from FDA, 2007, compiled by ERG.

ERG also calculated total sponsor and competitor conflicts separately, as well as a weighted total conflict measure based on whether conflicts were direct or imputed to the individual and ongoing or past relationships. These calculations are not shown, since data analysis results did not differ significantly by the different ways of measuring conflict.

5. MEASURING EXPERTISE

Quantifying expertise is a challenging and inherently limited undertaking. It is difficult, if not impossible, to adequately summarize an individual's personal accomplishments and lifetime contributions to scientific endeavors in numbers alone. Given this limitation, ERG attempted to use straightforward measures of expertise assumed to be analogous across individuals already identified as experts in their fields by the nature of their appointment to FDA advisory committees. The conclusions made in this study and the data on which those conclusions are based are a function of the criteria and assumptions under which the study was conducted.

Highly expert individuals are often in demand as consultants to regulated industry, leading to potential conflicts of interest (McComas, et al., 2005). FDA is interested in exploring whether it is possible and practically feasible to assemble hypothetical advisory committees with members who have equivalent expertise to current members, but who have no conflicts of interest. Therefore, it is necessary to develop measures of expertise which allow for comparisons and rankings of individuals.

Members of FDA advisory committees, by definition, are experts in their fields. Even among such a highly qualified group, however, there are variations in the level of overall expertise. A number of measures are routinely used to evaluate faculty performance for tenure and promotion decisions (see, e.g., Arreola, 2000; Bland, et al., 2002; Hasselback, et al., 2000; Kurz, et al., 1989). These are typically standardized and comparable across faculty members. Some require additional elaboration of measures found on curriculum vitae (CVs). While this is generally not a problem at a single institution, our analysis is limited to the information available on the CVs for individuals in our sample.

CVs for most FDA advisory committee members are available on the FDA advisory committee website (http://www.fda.gov/oc/advisory/default.htm). For the purposes of this study, FDA staff provided to ERG paper copies of CVs that were not posted on the website. In addition to curriculum vitae or resumes, ERG utilized the Thompson Web of Science® database to generate additional measures of expertise. Web of Science® is an index of publications from 8,700 highly-regarded research journals. Its Science Citation Index® lists journal articles from 1900 to the present.[12] The database can be utilized as a search engine to identify articles related to a particular topic of interest. It also features cited reference searching and citation analysis. These tools allow a researcher to quantify how often an author's papers

[12] For more information, see http://scientific.thomson.com/products/wos/. We accessed the Web of Science® database through Tisch Library at Tufts University, Medford, MA. See Appendix A for information regarding the methods used to collect data from the Web of Science®.

are cited and by whom. No additional information was available to ERG for the purposes of estimating advisory committee member expertise.

Using the faculty evaluation literature as an initial guide, we compiled a list of possible qualitative measures of general expertise. Once we began collecting data, we found that people in our sample reported these measures in different ways on their CVs. Without additional information, we could not be confident in accurate comparisons across people for some of our proposed measures. We discuss the specific variables and data problems in the next section. We collected the following data from individuals' CVs:

- Academic title
- Year of graduation for advanced degree
- Year of panel appointment
- Years of academic experience
- Years of clinical experience
- Years of other pertinent experience
- Total grants, including those funded by industry, government, and non-profits
- Total refereed publications, book chapters, books authored, books edited, abstracts, and other publications

We also collected the following data from Thomson's Web of Science® database:

- Total citations
- Total citations not including self-citations
- Average citations per publication
- H-index

5.1 EXPLANATION OF VARIABLES

The variables included in our analysis were chosen as broad measurements of overall expertise. We include only those variables that were available and comparable for all advisory committee members. The time and resource limitations of our study preclude the more detailed comparison of expertise at the level of the specific topics considered in advisory committee meetings. This limitation is significant.

Academic Title: In our initial analysis, we included a numerical ranking of academic title (i.e., professor, assistant professor, etc.). We found, however, that this variable did not add useful information to our analysis, so it is not included in the results presented below.

Total Years of Experience: We calculated the variable "years of experience" by subtracting the year of graduation from the year of appointment to the panel. Year of appointment or selection for the panel was considered the relevant year for evaluating expertise. For some individuals either the year of appointment or year of graduation was missing. In the former cases, we used the year of the meeting as the year relevant for evaluating expertise. In the latter cases, we were often able to calculate years of experience using dates of employment from the person's CV. For these individuals, we used the maximum years of academic, clinical, or other experience.

Years of Clinical Experience: Years of clinical experience was calculated from CVs by summing the total years of employment in a hospital or other clinical setting where the expert was likely to be directly engaged in patient care. This included academic positions where the expert was affiliated with a teaching hospital. In all cases, clinical experience was either less than or equal to total years of experience.

It should be noted that the length of time spent performing a task is not always correlated with the expertise acquired therein. In many industries, however, years of experience are a generally accepted measure of the accumulated knowledge of an individual over time. ERG uses years of experience as a readily available and commonly accepted proxy to objectively quantify the expertise of individuals already identified as "experts" by the nature of their appointment to an FDA advisory committee.

Total Grants: We excluded grants from the final expertise analysis because many of the individuals in our sample truncated the number of grants shown on their CVs, and others appeared not to have listed grants on their CVs. Thus, we were not confident in the accuracy and comparability of this measure.

Total Publications: Due to format variations among CVs in the sample, we were unable to compare types of publications (e.g., refereed vs. other publications). Therefore, we summed all publications listed on the CV as it was presented to ERG.[13] Time and resource limitations impede a more complex assessment of an individual's publication record. Comparisons of total publication counts as

[13] The count of total publications may include peer-reviewed and non-peer reviewed articles, book chapters, books authored, books edited, book reviews, presentations, monographs, workshop reports, other publications, and abstracts.

listed on CVs to the total publications listed in journal databases like Entrez PubMed or Thompson's Web of Science® are inconclusive. Journal databases do not cover books, book chapters or other non-journal publications that might represent a significant contribution of an individual to a scientific discipline. In addition, it is often difficult to separate publications in citation databases by author name for individuals who have common surnames and first initials. For the purposes of this study, it is assumed that the CV provided to FDA by an advisory committee member is an accurate representation of the experience which qualifies the individual to serve on an advisory committee. If, however, an individual truncated their list or was less inclined than another to list certain types of publications, this measure may underestimate their total number of publications.

Citations: Total citations and average citations per publication, by author, are available from Thompson's Web of Science®. However, the difficulty in differentiating publications for authors with similar names again presented a significant limitation. Ensuring the accuracy of citation counts for each author would require verification that every publication identified by Web of Science® truly belonged to the author in question. In the sample, total number of publications per author ranges from 0 to 722, with a median publication count of 132. The total number of publications for all 124 advisory committee members in the sample is 21,123. ERG has no reason to believe that total or average citation counts are any more indicative of expertise than any other measure and thus determined that the potential benefit of accurate total or average citation counts did not outweigh the effort required to generate them.

H-index: H-index was chosen as an overall measure of citations and scholarly impact. "A scientist has index *h* if *h* of his/her N_p papers have at least *h* citations each, and the other (N_p – *h*) papers have no more than *h* citations each" (Hirsch, 2005). "The index is designed to improve upon simpler measures such as the total number of citations or publications, to distinguish truly influential scientists from those who simply publish many papers. The index is also not affected by single papers that have many citations" (H-index, 2007). (See Appendix B for an example of the H-index calculation.)

Compared to total publication counts, values for H-index are generally lower (for instance, members in our sample have a median H-index of 21.5). Using the publication lists provided in an author's CV, we were able to determine with reasonable certainty that each publication used to calculate the H-index in Web of Science® was indeed an author's actual publication.

One important limitation of the H-index is that "citation patterns vary among scientific disciplines" (Kelly and Jennions, 2006). This might be particularly evident, for example, between the social and natural sciences. Although ERG recognizes that standing advisory committee members have varying subspecialties, sample size limitations prevent us from analyzing expertise by subspecialty or by

FDA Center. For the purposes of this study, ERG assumes that similar citation conventions exist within the overarching field of biomedical research. Further, the H-index is not utilized in this study as an independent test of expertise, but rather as one component of a broader measure of overall expertise.

Like Kelly and Jennions, ERG found that the H-index shows a significant gender effect. The mean H-index for male standing advisory committee members is 26.6, while the mean H-index for females is 17.2. H-index is highly correlated with total publications and, on average, the women in our sample had fewer publications than the men. The gender difference is further compounded by the fact that more women than men are consumer representatives. The H-indices for consumer representatives are lower than those members who are principally academicians or clinical practitioners. Our methods for addressing these concerns are described in the analysis below.

We based our final analysis on the following variables, which we felt could be reasonably compared across individuals in the sample:

- Total Years of Experience
- Years of Clinical Experience
- Total publications
- H-index

Table 5-1 shows summary statistics on the individual expertise measures compiled for all members. These measures were not used independently to compare members with waivers to members without waivers. The mean for total years of experience for members in our sample is 25.8 years, ranging from a minimum of 10 years to a maximum of 48 years. Mean years of clinical experience ranged from 0 years to 48 years, with a mean of 17.7 years. Total number of publications listed on CVs ranged from 0 to 722 publications with a mean of 170 publications. H-indices ranged from 0 to 78 with an average for all members of 23.8.

Table 5-1: Summary Statistics for Expertise Measures

	All Members (n=124)	Members With Waivers (n=32)	Members Without Waivers (n=92)
Total Years of Experience			
Mean (standard deviation)	25.8 (8.0)	28.3 (7.6)	25.0 (7.9)
Median	25.0	26.5	25.0
Minimum	10	15	10
Maximum	48	48	41
Years of Clinical Experience			
Mean (standard deviation)	17.7 (11.8)	20.9 (12.4)	16.6 (11. 4)
Median	18	22	16
Minimum	0	0	0
Maximum	48	48	38
Total Publications			
Mean (standard deviation)	170 (146)	233 (168)	149 (132)
Median	132	193	125
Minimum	0	11	0
Maximum	722	722	708
H-index			
Mean (standard deviation)	23.8 (16.2)	29.4 (15.6)	21.8 (16.0)
Median	21.5	30.5	19.0
Minimum	0	0	0
Maximum	78	60	78

Source: Compiled by ERG.

5.2 EXPERTISE INDEX AND RANKING

In order to compare or rank individuals by expertise, we constructed a composite index as an overall measure of expertise that incorporates the individual measures described in the previous section.

5.2.1 Composite Index

A composite index combines various measures into a single number, by first rescaling the measures to a common scale, and then combining them. A well-known and respected composite index is the UN's Human Development Index, a measure that compares the level of development of countries, as an alternative to GDP, using a combined measure of health, education, and income (Watkins, et al., 2005).

In order to combine individual measures, we first normalized the values for each measure (total years of experience, years of clinical experience, publications, and H-index) to adjust them to a single scale. Normalization (see, e.g., Jain, et al., 2005; Van Erp and Shomaker, 2000) changes the location and scale parameters of a set of values so that they are transformed to a common scale. We used the min-max

method (Anand and Sen, 1994), the method used to calculate the UN's Human Development Index (UNDP, 2006). It shifts values to the 0-1 scale, using the following formula:

$$\text{normalized value, } x'_i = (x_i - \min)/(\max - \min)$$

where x_i is the raw value for each individual person, i, min equals the minimum value in the sample, and max equals the maximum value in the sample. This method is best suited for the case where bounds of scores are known. It retains the original distribution of scores, except for a scaling factor. Its primary weakness is its sensitivity to outliers.

To check for outliers, we applied the interquartile range test (Berk and Carey, 2004). This test is based on measuring the width of the center of the distribution (the interquartile range) and then adding a specified amount to each end, in order to determine values that fall far from the center of the distribution. Unlike some outlier tests, it does not require the assumption of a normal distribution.

First, we calculated the difference between the first and third quartiles, the interquartile range, for each of the three expertise measures. Then we checked for moderate or extreme outliers. A moderate outlier is any value greater than the third quartile plus 1.5 times the interquartile range, or less than the first quartile minus 1.5 times the interquartile range. An extreme outlier is any value greater than the third quartile plus 3 times the interquartile range, or less than the first quartile minus 3 times the interquartile range.

Our sample had no outliers for years of experience. There were 8 moderate and 2 extreme outliers for publications; and one moderate outlier for the H-index. Half the outliers were individuals with waivers and half were individuals without waivers. Since the outliers offset each other in comparing those with and without waivers, we did not adjust the outliers or eliminate them from our sample.

Once the values were normalized, we combined them into an index using a simple average of the individual normalized values. While it might make sense to use weighted averages, as some of the tenure evaluation systems do, we had no information on which to base our choice of weights. Therefore, the indices weight each measure equally.

In our initial analysis, our composite index of expertise included the normalized values for total years of experience, publications, and H-index. Due to the gender differences in the means for these individual measures of expertise, the expertise index was higher for men (0.34) than for women (0.27), which is statistically significant at the 5 percent level ($t= 2.39$, $p= 0.019$). This gender difference is partially due to the differences in numbers of publications and the H-index for consumer representatives.

Although the consumer representatives have similar total years of experience in comparison to academic members, they tend to have fewer publications. In our sample, seven of nine consumer representatives were women.

Given the limitations to quantifying expertise similarly across member types, we temporarily removed standing consumer representatives from the sample. This step slightly reduces the difference in the mean expertise index between genders: the expertise index for women increases to 0.30 and remains at 0.34 for men. Without standing consumer representatives, the difference in mean expertise index between men and women is no longer statistically significant at the 5 percent level (t= -1.41, p= 0.162).

In an attempt to keep the standing consumer representatives in the sample, we added the normalized variable for years of clinical experience to the expertise index. The addition of this variable offsets the gender difference in publication records by giving additional significance to years of experience. With consumer representatives in the sample, the inclusion of clinical experience results in a mean expertise index of 0.30 for women and 0.35 for men, and the difference is not statistically significant (t= 1.65, p= 0.102). Since the inclusion of this variable makes later data analysis results more robust, ERG chose to use the modified expertise index (including years of total experience, years of clinical experience, publications, and H-index) and keep the standing consumer representatives in the sample. ERG also conducted a sensitivity analysis to assess the effect of uncertainty concerning the most appropriate model structure on the index values (see Appendix C). The purpose of the sensitivity analysis is to ensure that the expertise index is not correlated with or dependent on a single variable or component of the index. The relative lack of sensitivity in the expertise measure suggests that all four variables contribute to the model.

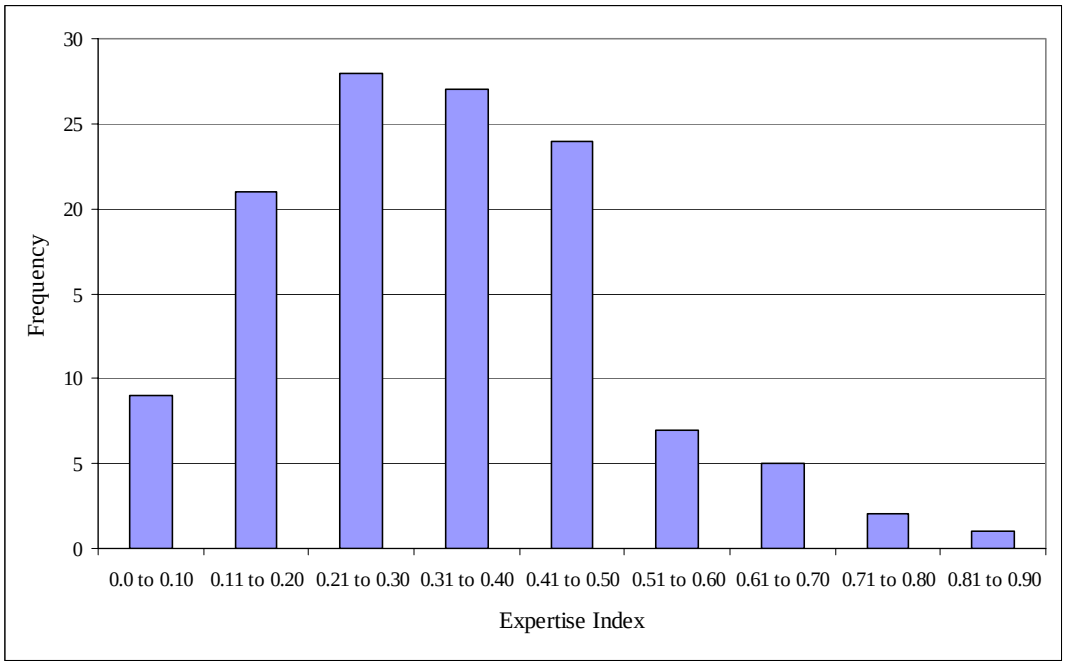
Summary statistics for the expertise index values are shown in Table 5-2. Figure 5-1 shows the raw frequency distribution of expertise index for our sample. Figure 5-2 compares the relative frequency distribution of expertise index for members in the sample with and without waivers.

Table 5-2: Summary statistics for Min-Max Expertise Index, (includes standing consumer representatives)

	All Members (n=124)	Members With Waivers (n=32)	Members Without Waivers (n=92)
Mean (standard deviation)	0.33 (0.16)	0.40 (0.15)	0.31 (0.16)
Median	0.32	0.38	0.29
Minimum	0.02	0.14	0.02
Maximum	0.81	0.77	0.81

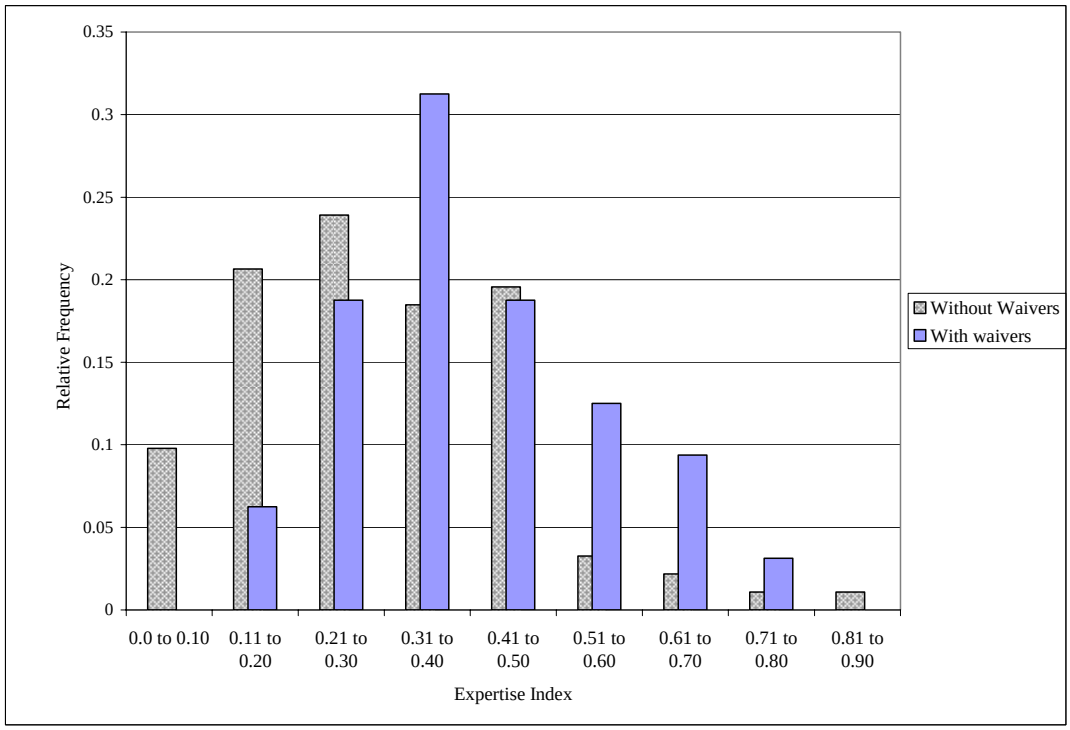
Source: Compiled by ERG.
Note: The expertise index is the simple average of the normalized counts of total years of experience, years of clinical experience, total publications, and H-index.

Figure 5-1: Frequency Distribution of Expertise Index



Source: Compiled by ERG.
Note: The expertise index is the simple average of the normalized counts of total years of experience, years of clinical experience, total publications, and H-index.

Figure 5-2: Relative Frequency Distribution of Expertise Index for Members With and Without Waivers



Source: Compiled by ERG.
Note: The expertise index is the simple average of the normalized counts of total years of experience, years of clinical experience, total publications, and H-index.

5.3 COMPARISONS OF MEMBERS BASED ON WAIVERS

To assess the relationship between overall expertise and waivers, we compared the sample mean of the expertise index for members with waivers versus members without waivers, using t-tests. The t-statistic is calculated as:

$$t = \frac{(\overline{x_1} - \overline{x_2}) - (\mu_1 - \mu_2)}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

where x_1 and x_2 are the sample averages, s_1 and s_2 are sample standard deviations, n_1 and n_2 are the sample sizes, and μ_1 and μ_2 are the means of the distributions. The t-test results are presented in Table 5-3.

For our sample, the members with waivers had a mean expertise index of 0.40, while those without waivers had a mean expertise index of 0.31. Based on these calculations, the mean expertise of those with waivers is statistically significantly greater than those without waivers. Thus, based on the methodology used in this report to measure expertise, it appears that committee members with waivers have, on average, more expertise than those without waivers. This result supports the premise of the "shared pool dilemma." In other words, the result suggests that highly-expert clinical and academic researchers are often those in demand by both FDA and regulated industry.

Table 5-3: Comparisons of Sample Means for Expertise Index

	Members With Waivers (n=32)	Members Without Waivers (n=92)
Mean	0.40	0.31
Variance	0.023	0.025
Degrees of freedom	56	
t statistic	3.06	
P(T<=t), two-tail	0.003*	

Source: Compiled by ERG.
* statistically significant at $\alpha = 0.05$

How do these results for the comparisons of the overall index relate to the four actual measures of expertise used to create the index (i.e., years of experience, years of clinical experience, total publications, or H-index)? *Evaluated at the mean for the sample*, the following can be inferred from these results:

Holding all else equal, a 0.09 increase in the overall expertise index could be brought about either by:

- An increase in years of experience by 13.7 years; or

- An increase in years of clinical experience by 17.3 years; or
- An increase in total publications of 260; or
- A rise in the H-index of 28.1. [14]

It is important to note that the normalized values for each variable and, therefore, the individual values of the expertise index are sample-dependent. The results presented above are, therefore, also sample-dependent and evaluate the impact of a unit change in each variable at the mean for the group. These results should only be considered in this context. They should not be used to describe the relationship between specific experts or their individual measures of expertise either within the sample or beyond. The individual experts differ greatly in the combinations of the different measures that go into the index. For example, one expert with an index of 0.42 has 24 years of total experience, 24 years of clinical experience, 296 publications, and an H-index of 32. Another expert with an overall index of 0.32 has 24 years of total experience, 20 years of clinical experience, 140 publications, and an H-index of 25.

Due to the limitations noted earlier, this analysis is conducted using an overall measure of expertise; the relationship between topic-specific expertise and the likelihood of being granted a waiver should not be extrapolated from this analysis. In addition, our sample size prevents us from accurately comparing the expertise of those with and without waivers for each FDA Center individually.

[14] The methodology used to generate these results is presented in Appendix E.

6. CORRELATIONS BETWEEN MEASURES OF EXPERTISE AND CONFLICT OF INTEREST

To determine the nature of the relationship between expertise and conflict of interest, we calculated correlations between the expertise measures and dollar values of conflicts. There are 32 individual committee members in the conflict database and a total of 46 recorded conflicts (waivers).

The usual measure of correlation, the Pearson correlation coefficient, relies on the assumption of a normal distribution (skewness and kurtosis equal or close to zero), and is most appropriate for linear relationships between variables. Based on Figure 4-1, as well as measures of skewness ($\gamma_1 = 1.58$) and kurtosis ($\gamma_2 = 1.27$), the total dollar values of conflicts in our sample are not normally distributed.[15] The distribution is right-skewed, meaning that the average dollar value of conflict is disproportionately affected by a few very high dollar conflicts.

Since the distributions in our analysis are non-normal, we calculated correlations using two non-parametric measures, Kendall's tau-b and Spearman's rho.[16] Both measures evaluate the association between ranks which are assigned to the numerical values for each variable in the analysis, and thus do not rely on particular distributional assumptions. These measures also allow for non-linear relationships between the variables. Ranks of 1 through 46 were assigned to our measures of expertise and total dollar value of conflict for each record in our sample, where 1 is the individual with the lowest value, 2 the next lowest, and so on.[17]

Kendall's tau-b is measured by:

$$\tau_b = (C - D)/ \sqrt{[((C + D + Y_0)(C + D + X_0))]}$$

where C equals the number of concordant pairs, D equals the number of discordant pairs, X_0 equals the number of pairs not tied on X, and Y_0 equals the number not tied on Y.

Spearman's rho, measured by:

$$\rho = 1- [6\sum(d_i)^2) / (n(n^2 – 1)]$$

---

[15] Skewness is a measure of the asymmetry of a distribution. A normal distribution is symmetrical (identically shaped to the left and the right of the center point) and has a skewness of zero. Positive skewness indicates that the distribution is right-skewed, with a data points to the left of the mean that give the distribution a long right tail. Kurtosis measures whether the data are peaked or flat relative to a normal distribution, where a distribution with a positive kurtosis indicates that the data is peaked near the mean rather than flat.

[16] Nonparametric statistical methods do not rely on assumptions about the frequency distributions of the variables.

[17] In situations where ties exist, we used the average rank.

where d_i equals the difference between the ranks assigned to x_i and y_i, and n equals the number of pairs.

The values for both Kendall's tau-b and Spearman's rho range from -1 to +1. Values of 1 indicate perfect correlation between the rankings, with +1 occurring for identical rankings and -1 occurring for reverse rankings.

The correlation coefficients and significance levels are shown in Table 6-1.[18] The table presents results for total dollar value of conflicts for each waiver. We obtained similar results for separate sponsor and competitor conflict totals, and for weighted total conflicts (weights were assigned to direct and indirect, sponsor and competitor conflicts). Those results are not presented in this report.

Table 6-1: Correlations between Total Dollar Value of Conflict and Various Expertise Measures

Total conflict ($) vs.:	Kendall's tau-b	Spearman's rho
Total years of experience	-0.124 (0.241)	-0.186 (0.217)
Years of clinical experience	-0.090 (0.392)	-0.126 (0.405)
Total publications	-0.075 (0.471)	-0.095 (0.531)
H-index	-0.149 (0.152)	-0.204 (0.174)
Expertise index	-0.143 (0.166)	-0.186 (0.217)

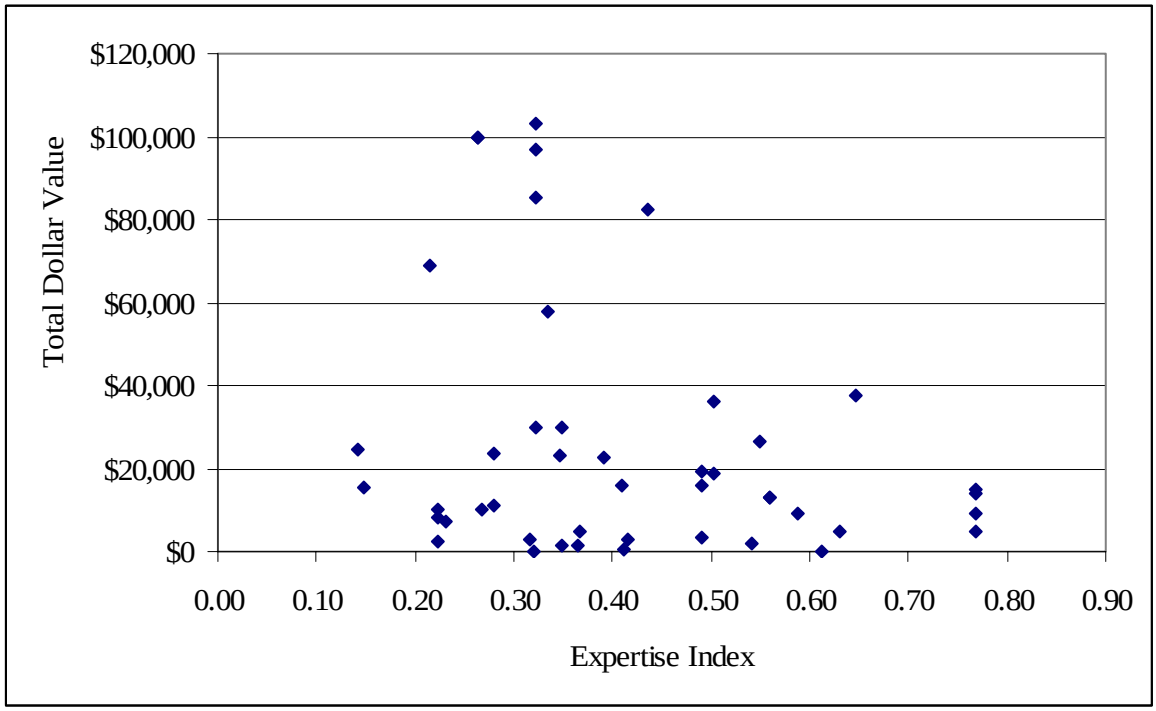
Source: Compiled by ERG.
Note: Significance level in parentheses.

For each measure of expertise in Table 6-1, the values of both Kendall's tau-b and Spearman's rho are negative and close to zero with relatively small variances. This suggests that the actual total dollar magnitude of conflicts is not significantly correlated with our measures of expertise.[19] This does not negate the significance of our previous finding that members with higher measures of expertise were more likely to have waivers. Rather, these results highlight the complexity and wide variability in the nature and magnitude of advisory committee members' financial conflicts of interest. The relationship between expertise and dollar value of conflicts in our sample is illustrated in Figure 6-1.

One limitation of our dataset, however, is that these waivers and associated financial conflicts are meeting-specific. They are obtained from FDA Form 3410, on which advisory committee members list their financial interests in products, firms, and issues as they pertain to a particular meeting and agenda. Therefore, our data may or may not represent an individual's broader financial ties to industry. Further investigation may be needed to explore this possibility.

[18] Correlations were calculated using the non-normalized values for years of experience, publications, and H-index.
[19] Correlations did not differ significantly by the different methods of measuring conflict.

Figure 6-1: Total Dollar Value of Conflict by Expertise Index



Source: Compiled by ERG.

7. HYPOTHETICAL COMMITTEES WITHOUT CONFLICTS

FDA is interested in whether it is possible to assemble advisory committee meetings composed of highly qualified individuals, none of whom require a waiver for potential conflict of interest. In order to assess this possibility, we attempted to create hypothetical rosters for a sub-sample of committee meetings in our larger sample. This component of the study had two separate objectives:

1. To determine whether it is possible to identify qualified surrogate committee members who would not require waivers, where such individuals have equivalent or greater expertise than committee members with waivers; and
2. To evaluate whether it is practical to do so, in terms of the time and effort required.

For this analysis, we selected the four meetings from our original sample with the highest numbers of waivers granted to participants. Based on the prevalence of financial conflicts, these types of meetings present the greatest challenges to FDA regarding the identification of alternative participants. Table 7-1 shows statistics on the sub-sample. See Appendix B for more detailed information on the 17 individuals in the sub-sample who received waivers. All of the meetings selected were for the Center for Drug Evaluation and Research.

Table 7-1: Meeting Sample Used for Identifying Hypothetical Alternative Committee Rosters

Total Standing Members [a]	Total Consumer Reps. [b]	Total Temporary Voting Members (including Patient Reps.)	Total Waivers	Waivers for Members	Waivers for Consumer Reps.	Waivers for Temporary Voting Members (including Patient Reps.)
CDER *Oncologic Drugs Advisory Committee* 9/6/2006 – 9/7/2006, Fragmin, Genasense, Abraxane						
6	1	13	8[c]	4	1	3
CDER *Joint meeting of the Nonprescription Drugs and Endocrinologic & Metabolic Drugs Advisory Committees* 1/23/2006, Orlistat						
12	0	0	6	5	0	1
CDER *Peripheral and Central Nervous System Drugs Advisory Committee* 3/7/2006, Tysabri						
8	1	1	5	4	1	0
CDER *Joint meeting of the Nonprescription Drugs and Pulmonary-Allergy Drugs Advisory Committees* 1/24/2006, CFC's in epinephrine MDIs						
14	2	2	4	3	0	1

[a] Not including industry representatives or consumer representatives who are standing members (see Note b).

[b] Includes those consumer representatives that are standing committee members.

[c] Includes 5 individuals with multiple waivers for different topics.

7.1 EVALUATING EXPERTISE FOR POTENTIAL CANDIDATES

Ideally, individuals who could hypothetically replace the meeting participants holding waivers would be surrogates with perfectly matched qualifications. We used several methods for identifying qualified surrogates.

ERG attempted to closely match potential alternatives with the committee member requiring a waiver. To do this, we searched for candidate experts by area(s) of specialization, as indicated on the FDA Advisory Committee website roster. For more specific areas of expertise, we used the waiver documentation available online. This document generally describes the individual's expertise as it relates to the necessity of the waiver. To guide our searches, we also used academic and clinical titles, publications in specific topic areas, and board certifications.

For our complete sample, we evaluated overall expertise using the following general expertise measures: total years of experience, years of clinical experience, publications, and H-index. Using these measures, we calculated a normalized expertise index for each individual. We utilized this index as a benchmark to identify potential surrogate candidates whose overall expertise was at or above the average for the individuals with waivers. Specifically, we looked for people whose expertise index was greater than or equal to the sample mean expertise index for individuals with waivers (expertise index > 0.40).[20] This was not possible in a few cases. For example, our methodology identified only one scholar in the area of health literacy that had a higher estimated expertise index than the advisory committee member with a waiver. In these cases we attempted to identify individuals whose expertise index was greater than or equal to the expertise index of the person they would hypothetically replace, or the most promising candidates based on other apparent qualifications.

7.1.1 Finding experts

We began our search for alternative candidates using the Internet search engine Google Scholar, as well as the advanced search functions within Web of Science®. These tools allowed us to search for people with large numbers of publications in the relevant topic area(s). Specifically, we generated Web of Science® analysis reports on the most cited authors by specific topic area or for relevant peer-reviewed journals. To augment our search, we also relied on ISI's Highly Cited Researchers database and on the websites of medical schools and medical centers known for their expertise in the relevant topic areas.

[20] Years of clinical experience were not readily available, so this measure was not included in the calculation of expertise index for the alternative candidates. This is not expected to have a significant impact on our findings.

Publications listed in Web of Science® are assigned to a category by topic area. Once you have identified an author, the database will provide the number of publications in each topic area. This represents a broad generalization of the author's major disciplines. For example, the members of the Peripheral and Central Nervous System Drugs Committee at the meeting session for Tysabri are all highly published in the Web of Science® topic area of 'Clinical Neurology.' Many are also highly published in 'Neurosciences.' Each individual might have secondary specialties, such as 'Peripheral Vascular Disease' or 'Psychiatry.'

To identify possible replacement candidates, ERG used the Web of Science® advanced search function to identify all publications categorized in the major topic areas identified for each member with a waiver in the sample.[21] Then, using the analyze results feature, ERG ranked the resulting publications by author and sorted them by record count. This allowed us to generate a ranked list of authors by number of publications in each identified topic area. Other major topic areas included 'biostatistics,' 'endocrinology and metabolism,' 'pulmonary disease,' and 'clinical pharmacology.'

Once candidates who are highly published in relevant areas of specialization were identified, we further screened individuals utilizing Internet searches. The screening process involved a search for a personal website, curriculum vitae, or biography that might provide further insight into their level of expertise, including their specialty, years of experience, and other qualifications. Identifying conflicts of interest was not the intention of this preliminary screening process. We did, however, note those individuals who appeared to have large, ongoing financial ties to industry based on any available information. In these cases, additional candidates were identified to offset those with readily apparent conflicts. For the purposes of this study, all individuals were identified without regard to geographic, gender, or ethnic diversity.

For promising candidates, ERG acquired the information necessary to quantify their general expertise according to our methodology for the full sample. These measures include years of experience, number of publications, and H-index.[22] When available, we used biographies on relevant institutional websites or personal homepages, curriculum vitae, or the Highly Cited Researchers database. In most cases, years since graduation from medical school or graduate school was used as a proxy for years of experience. When an actual count of publications was not available, we used the number of publications

[21] Web of Science® search functions return up to 100,000 entries.
[22] Years of clinical experience for potential alternative candidates were not available; therefore, they were not included in the overall expertise index.

appearing in Entrez PubMed.[23] Since not all publications appear in PubMed, such as books and book chapters, the number of publications from PubMed is an underestimate of an individual's total number of publications. In addition, the calculated H-index from Web of Science® is also approximate and likely to be underestimated because we did not always have a curriculum vita with which to compare actual publication titles with those that appear in Web of Science®. However, no personal contact with a potential candidate or their institution was required for our estimates.

Given the nature of the study, we were not able to assess the candidates' willingness to participate in the FDA advisory process. Further, we had no information with which to assess whether individuals might be well-suited to the advisory committee process, by reason of their interests, tolerance for the deliberative processes, willingness to work with FDA and others to resolve issues, personal histories with other committee members, or any other personal factors that might affect their fit on a committee. In addition, as noted above, potential candidates were identified without regard to geographic, gender, or ethnic diversity – factors that would be important in achieving fair balance goals under the Federal Advisory Committee Act. Although ERG recognizes that these elements impose a significant limitation of the study, this methodology is not dissimilar to the initial steps in the recruitment methods currently in place at FDA, whereby the credentials of advisory committee nominees are reviewed by Agency staff to assess a candidate's relevant qualifications.

In total, we identified 70 potential alternative candidates, including at least three possible surrogates per current member in the sub-sample that required a waiver. For each candidate located, there were a number of others identified that did not qualify based on our measures of general expertise. ERG estimates that it took approximately 88 hours in order to generate our final selection of 70 possible alternatives. This includes the time necessary to narrow our extensive initial search results to a shorter list of approximately 212 experts who were then investigated more closely. Table 7-2 shows expertise measures for the 17 individuals with waivers in our sample and for their potential substitutes.

Although ERG did not stratify our search based on geographic, ethnic or gender diversity, the final list of alternatives does include both male and female experts from reputable institutions across the country. No assumptions are made about ethnic diversity.

In section 5.3 of this report, ERG finds that standing advisory committee members who were granted waivers are more likely to have higher levels of overall expertise than those members not granted waivers. The average overall expertise index for standing advisory committee members in our sample

[23] PubMed is a service of the U.S. National Library of Medicine and the National Institutes of Health.

who were granted waivers is 0.40. The average overall expertise index for the 70 possible alternative candidates is 0.54. Our findings indicate that it may be possible to identify individuals with equivalent or greater overall expertise than current advisory committee members. There is also a significant possibility that many of the 70 surrogate candidates identified are just as likely to have financial ties to regulated industry. The following section describes the likelihood of financial conflicts for the 70 possible alternatives.

Table 7-2: Expertise Qualifications for Members with Waivers and Replacement Candidates

	Topic Searched	Degree	Approximate H-index	Publications	Total Years of Experience	Min-Max Index
*	Member	MD	43	217	35	**0.560**
*	Member	MD	60	361	34	**0.647**
*	Member	MD, PhD	48	511	34	**0.630**
1	Pharmacology	MD	88	952	-	**1.395**
2	Clinical pharmacology	PhD	107	655	33	**1.078**
3	Clinical pharmacology	PhD	52	388	41	**0.762**
4	Clinical pharmacology	PhD	50	331	36	**0.640**
5	Pharmacology	PharmD	53	256	31	**0.571**
6	Pharmacology	PhD	32	369	-	**0.518**
7	Pharmacology	MD, PhD	44	203	-	**0.502**
8	Clinical pharmacology	PhD	44	170	32	**0.478**
9	Pharmacology	PharmD	26	422	27	**0.458**
10	Pharmacology	PhD	29	216	27	**0.413**
11	Pharmacology	MD	40	112	-	**0.404**
12	Clinical pharmacology	PharmD, PhD	28	234	27	**0.381**
*	Member	MD	20	129	26	**0.349**
1	Endocrinology	MD	114	-	38	**1.171**
2	Endocrinology	MD	84	342	41	**0.884**
3	Endocrinology	MD	69	679	32	**0.868**
4	Endocrinology	MD	58	208	31	**0.576**
5	Endocrinology	MD	56	286	36	**0.652**
6	Endocrinology	MD	52	141	29	**0.491**
*	Member	MD	51	471	30	**0.588**
*	Member	MD	32	337	24	**0.410**
*	Member	MD	0	11	19	**0.141**
*	Member	MD	34	140	19	**0.279**
*	Member	MD	42	346	21	**0.415**
1	Clinical neurology	MD, PhD	92	564	30	**0.922**
2	Clinical neurology	MD	73	402	-	**0.883**
3	Clinical neurology	MD	73	398	32	**0.759**
4	Clinical neurology	MD	73	337	33	**0.740**
5	Clinical neurology	MD	67	479	29	**0.733**
6	Clinical neurology	MD	51	407	28	**0.600**

	Topic Searched	Degree	Approximate H-index	Publications	Total Years of Experience	Min-Max Index
7	Clinical neurology	MD	61	234	26	**0.555**
8	Clinical neurology	MD	35	312	-	**0.503**
9	Clinical neurology	MD	50	212	28	**0.503**
10	Clinical neurology	MD, PhD	45	130	-	**0.496**
11	Clinical neurology	MD	27	302	34	**0.478**
12	Clinical neurology	MD	43	151	31	**0.466**
13	Clinical neurology	MD	44	314	22	**0.457**
14	Clinical neurology	MD, PhD	35	147	30	**0.410**
15	Clinical neurology	MD	26	125	15	**0.215**
16	Clinical neurology	MD	21	58	20	**0.189**
*	Member	MD, MS	7	39	15	**0.147**
1	Pulmonary/asthma	MD	75	474	34	**0.814**
2	Pulmonary/asthma	MD	63	437	34	**0.742**
3	Pulmonary/asthma	MD	60	305	31	**0.633**
4	Pulmonary/asthma	MD	38	198	35	**0.501**
5	Pulmonary/asthma	MD	29	153	35	**0.499**
6	Pulmonary/asthma	MD	30	104	34	**0.402**
*	Member	MD	21	91	24	**0.316**
1	health literacy	MD	34	289	25	**0.420**
2	health literacy	MD, MPH	32	121	21	**0.290**
3	health literacy	PhD	35	173	16	**0.280**
4	health literacy	MD	20	53	21	**0.191**
5	health literacy	PhD	17	66	14	**0.110**
6	health literacy	MD	10	29	15	**0.079**
*	Member	PhD	52	200	30	**0.367**
*	Member	PhD	31	93	30	**0.263**
1	biostatistics	PhD	52	363	37	**0.676**
2	biostatistics	PhD	45	197	36	**0.549**
3	biostatistics	PhD	43	123	32	**0.463**
4	biostatistics	PhD	39	119	31	**0.429**
5	biostatistics	PhD	52	224	18	**0.419**
6	biostatistics	PhD	27	45	40	**0.418**
7	biostatistics	PhD	42	119	26	**0.395**
*	Member	RN	1	47	26	**0.224**
1	Oncology nursing	RN, PhD	20	128	40	**0.418**
2	oncology nursing	MSN, PhD	18	134	31	**0.319**
3	oncology nursing	RN, DNSc	11	84	31	**0.257**
4	oncology nursing	PhD, MPH	17	66	20	**0.171**
5	oncology nursing	RN, PhD	11	47	21	**0.139**
*	Member	MD	46	722	37	**0.768**
*	Member	MD	19	141	24	**0.322**
*	Member	MD	29	270	34	**0.490**

	Topic Searched	Degree	Approximate H-index	Publications	Total Years of Experience	Min-Max Index
1	Oncology or hematology	MD	95	607	34	**0.999**
2	Oncology or hematology	MD	48	207	50	**0.849**
3	Oncology or hematology	MD	64	423	36	**0.761**
4	Urology, oncology	MD	47	596	27	**0.657**
5	Urology, oncology	MD	55	336	32	**0.630**
6	Oncology or hematology	MD	47	259	38	**0.610**
7	Oncology or hematology	MD	40	269	37	**0.565**
8	Oncology or hematology	MD	45	170	-	**0.487**
9	Urology, oncology	MD	47	247	25	**0.473**
10	Oncology or hematology	MD	35	198	33	**0.464**
11	Urology, oncology	MD	34	289	25	**0.420**
12	Oncology or hematology	MD	27	299	26	**0.396**

Source: Compiled by ERG.

7.2 EVALUATING CONFLICTS OF INTEREST FOR POTENTIAL CANDIDATES

Section 7.1 identified 70 highly qualified candidates with expertise similar to current advisory committee members with waivers. In order to determine the possibility of creating hypothetical committees that do not require waivers, we attempted to assess the financial conflicts of interest for the 70 alternative candidates. To do so, we provided our list of candidates to FDA. Through publication searches, FDA identified whether conflicts of interest were disclosed in publications authored by these candidates.[24] This process was repeated for the sub-sample of 17 current advisory committee members who have received waivers. FDA and ERG prepared the remainder of this section collaboratively.

FDA identified each author's publications using Entrez PubMed and then reviewed the articles for conflict of interest financial disclosures. Any journals that were unavailable via PubMed were cross-referenced in the FDA Biosciences Library database. If neither source produced any information for the articles listed, candidate names were then searched in the Google search engine. Conflicting financial disclosures were identified for all but a few of the authors using one or more of these methods.

The following four criteria are used to assess the results of the literature searches:

Financial conflicts disclosed: This category includes authors who have a financial relationship with a pharmaceutical company, either via consulting, speakers' bureaus, or stock or equity ownership.

[24] Katherine Neckers of FDA carried out the literature search and analysis of these results.

Statement of no financial conflicts: This category includes authors who asserted in published articles that they had no financial conflicts to disclose.

Indirect financial conflict: This category includes members and candidates whose work was indirectly supported by a company or who received grants, whether restricted or unrestricted, from a company.

No information found: This classification simply means that no financial information is available. Either the author's articles were in journals not available on PubMed or the FDA Biosciences Library, or they listed no direct or indirect financial conflicts but lacked a positive assertion of no conflicts.

Out of the 17 current members and 70 candidates whose works were searched, FDA found disclosure information for all but seven in PubMed or the FDA Biosciences Library. For those seven authors, FDA did an additional search in Google and found information for three. No financial information is available for the remaining four authors (one current member and three candidates). Table 7-3 displays the results of the literature search for both advisory committee members and alternative candidates.

FDA found 30 alternate candidates with statements of no conflicts of interest. From those, we could in theory select substitutes for the 17 current members with waivers in all disciplines, with the exception of pharmacology. This conclusion is presented in Table 7-4.

The supply of alternative candidates identified by the literature search almost certainly overstates the availability of alternative committee members with no financial ties to pharmaceutical companies. As Table 7-3 illustrates, this search methodology fell considerably short of identifying all the conflicts for the 17 existing members with waivers. FDA found disclosures for only 11 of the 17 current committee members with waivers. In addition, three current members asserted a lack of conflicts and one member had no information in the published papers FDA consulted.

There are a number of possible reasons for the lack of congruence between the conflicts based on a literature search and the conflicts identified in waivers. First, the FDA identifies potential conflicts according to the parameters of the applicable statutes and regulations governing the advisory committee process. These statutes and regulations cast a broad net and require that financial relationships not uniformly recognized as conflicts of interest be included in the scope of disqualifying financial interests. For example, the individual's employer's stock holdings in an affected company would be imputed to him, even though the individual has no personal financial interest in the company. Second, assertions of no conflict might have been made before the financial interest arose or might have been small enough to

not merit disclosure but large enough for a waiver. Recent studies have also highlighted the insufficient enforcement of and compliance with the conflict of interest disclosure policies of prominent academic journals (Goozner, 2004; Krimsky, 2001).

Table 7-3: Conflicts of Interest for Advisory Committee Members and Alternative Candidates

Field of Expertise	Financial Conflicts Disclosed	Statement of no Financial Conflicts	Indirect Financial Conflict	No Information Found	Total
Current Members	-	-	-	-	-
Pharmacology	2	1	-	-	3
Clinical pharmacology	-	-	-	-	-
Endocrinology	1	-	-	-	1
Clinical neurology	4	-	-	1	5
Pulmonary/asthma	-	1	-	-	1
Health literacy	-	-	1	-	1
Biostatistics	-	1	1	-	2
Oncology nursing	1	-	-	-	1
Oncology or hematology	3	-	-	-	3
Urology, oncology	-	-	-	-	-
Sum for members	**11**	**3**	**2**	**1**	**17**
Candidates					
Pharmacology	6	1	-	-	7
Clinical pharmacology	3	1	1	-	5
Endocrinology	5	1	-	-	6
Clinical neurology	4	10	1	1	16
Pulmonary/asthma	4	1	1	-	6
Health literacy	3	2	1	-	6
Biostatistics	1	5	1	-	7
Oncology nursing	-	3	-	2	5
Oncology or hematology	2	6	-	-	8
Urology, oncology	4	-	-	-	4
Sum for candidates	**32**	**30**	**5**	**3**	**70**

Source: Compiled by FDA.

We therefore conclude that although the literature search may uncover financial interests that might lead to a waiver, the method clearly missed some financial conflicts substantial enough to require a wavier. Based on the possibility of nondisclosure and the accuracy rate of the literature search method for identifying financial conflicts of current members, we predict that some of the 30 candidates who asserted no conflicts would indeed require waivers.

Table 7-4: Possible Availability of Alternative Candidates with no Financial Conflicts of Interest

Field of Expertise	Current Members with Waivers	Candidates with no Financial Conflicts Asserted	Potentially Available Substitutes
Pharmacology	2	1	No
Clinical pharmacology	1	1	Yes
Endocrinology	1	1	Yes
Clinical neurology	5	10	Yes
Pulmonary/asthma	1	1	Yes
Health literacy	1	2	Yes
Biostatistics	2	5	Yes
Oncology nursing	1	3	Yes
Oncology or hematology	3	6	Yes
Urology, oncology	-	-	-
Total	**17**	**30**	

Source: Based on data from Table 7-3 and Appendix B.

We also conclude that this search methodology is of uncertain value for identifying advisory committee candidates with qualifications equivalent to current members but without conflicts of interest. Finding a committee with no financial ties to industry would require starting with a larger pool of candidates than FDA now uses and carrying out literature searches to exclude those with published disclosures. Additional rounds of screening would then be required to exclude any candidates who did not have published disclosures, but did have conflicts of interest within the scope of the laws and regulations that FDA administers. Separate, additional screening would be needed regularly as new topics arise. This procedure could theoretically generate conflict-free advisory committee members, but at much higher recruitment and screening costs than are currently expended. It is uncertain whether sufficient numbers of conflict-free advisory committee members with equivalent expertise could be identified to convene a conflict-free committee for any particular meeting. The additional screening would also take more time and might adversely affect the logistics and responsiveness of advisory committee operations. Advisory committees meet to discuss and make recommendations on important public health matters. The additional time required to screen candidates could significantly delay committee meetings and related FDA actions on major public health issues.

This analysis is limited by several considerations. First, without actually contacting the alternates individually, we cannot judge the final number that would require waivers or their appropriateness as committee members. (FDA might reasonably exclude a number of potential experts as being problematic to work with for a variety of reasons, and some FDA invitations might be rejected.) Second, the relative expertise of the alternative panel to an existing advisory panel is difficult to assess unless specific topics are defined. The difficulty of comparing more or less topic-specific expertise among individuals impedes

more definitive judgments of relative expertise. The results presented here are not a definitive test of the hypothesis that FDA can create conflict-free advisory panels equivalent in expertise to their existing committees. We regard this as a first look into this important question. Nevertheless, this exercise suggests that any group of equivalently qualified alternative participants in FDA advisory committees will have substantial conflicts of interest and is likely to require numerous waivers. The practical feasibility of creating conflict-free advisory committees remains uncertain.

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9. APPENDIX A: WEB OF SCIENCE® METHODOLOGY

Access ISI Web of Knowledge: Web of Science®.

On the homepage under "Select a search option," select 'Author Finder.'

Enter the last name of the individual and their first and middle initials, where possible. If no middle name is available, select the wildcard option for unknown middle initial: Last, First*. Be sure to include additional name variants, including additional middle initials (up to 3) and wildcards for unknown initials. Click 'next' to continue.

In most cases, narrow specifically to 'Life Sciences and Biomedicine' (for example, where most articles fall into that category only and the majority remainder are 'arts and humanities.' For some individuals, whose articles might have been published in other subject areas, simply click 'next' to continue.

In cases with common names or large numbers of articles, select institutions associated with the author by reviewing the curriculum vitae or resume. In some cases, such as those with only a few articles associated with a name, this step was skipped to ensure that all articles by that author were captured. Click 'finish' to continue.

On the 'Search Results-Summary' page:

Narrow to English only articles under 'Languages.' (This step should be skipped in cases where the individual was educated or worked in another country.)

Narrow to appropriate range of 'Publication Years' based on information from curriculum vitae. (For example, years prior to 1960 were excluded if the author listed their first publication as 1963.)

Narrow to appropriate possible 'Subject categories' based on author specialty. (For example, subjects such as material science, urban studies, and computer engineering were removed for cardiovascular experts).

View citation report. Use best professional judgment based on reviews of curriculum vitae to determine if the citation report is still likely to be showing publications by another author with the same name.

If so, return to 'Search Results-Summary' page and continue to narrow by 'Subject Category' and 'Institution' where possible. This step is aided by more detailed reviews of publications in the curriculum vitae. Identify cases where a same-named individual is associated with a particular institution not associated with the author in question.

Record the 'Results Found' or total number of reported publications associated with the author.
Record the number of publications which are 'articles' under 'Document Types.'
Click on 'Citation Report.'

Record the 'Sum of the Times Cited.'
Record the 'Average Citations per Item.'
Record the 'H-index.'

Review the records for the articles included in the H-index to ensure that they are the author's true publications. Use the curriculum vitae as guidance. The articles included in the H-index are those listed before the green horizontal line or the number of articles, h, that have at least h citations.

10. APPENDIX B: H-INDEX CALCULATION

"A scientist has index *h* if *h* of his/her N_p papers have at least *h* citations each, and the other (N_p – *h*) papers have no more than *h* citations each." (Hirsch, 2005)

Example:

Author A

Publications for Author A*	Citations per Publication
1	200
2	154
3	78
4	60
5	30
6	15
7	10
8	5
9	3
10	0

* The numbers in the publication column are the publications' ranks according to the number of citations.

In this example, Author A has index 7 (*h*) because 7 of his/her 10 (N_p) papers have at least 7 (*h*) citations each, and the other 3 (N_p – *h*) papers have no more than 7 (*h*) citations each.

11. APPENDIX C: SENSITIVITY ANALYSIS

For the purposes of this study, ERG assessed the expertise of advisory committee members using an expertise index composed of the following normalized variables: years of experience, years of clinical experience, total publications and H-index. These variables are described in detail in Section 5 of the report. ERG found that advisory committee members with waivers had a higher mean expertise index than members without waivers.

ERG also conducted a sensitivity analysis to assess the effect of uncertainty concerning the most appropriate model structure on the index values. The purpose of the sensitivity analysis is to ensure that the expertise index is not correlated with or dependent on a single component of the index. ERG constructed four additional expertise indices, each consisting of only three of the four original normalized variables, as follows:

- Sensitivity Analysis 1: years of experience, years of clinical experience, and total publications;
- Sensitivity Analysis 2: years of experience, years of clinical experience, and H-index;
- Sensitivity Analysis 3: years of experience, total publications, and H-index; and
- Sensitivity Analysis 4: years of clinical experience, total publications, and H-index.

ERG also conducted a final sensitivity analysis to assess the effect of using H-index as a proxy for scientific impact, rather than total citations per author.

- Sensitivity Analysis 5: years of experience, years of clinical experience, total publications, and total citations.

For each analysis, ERG compared the resulting mean expertise index for members with waivers to the mean expertise index for members without waivers. The results of this sensitivity analysis (presented in the table below) indicate that there is a statistically significant difference in expertise between members with and without waivers regardless of which variables are utilized to create the expertise index. The relative lack of sensitivity in the expertise measure suggests that all four variables contribute to the model.

Sensitivity Analysis for Alternative Measures of Expertise

	Primary Analysis[a]		Sensitivity Analysis for Alternative Measures of Expertise									
			Sensitivity Analysis 1[b]		Sensitivity Analysis 2[c]		Sensitivity Analysis 3[d]		Sensitivity Analysis 4[e]		Sensitivity Analysis 5[f]	
	Members With Waivers	Members Without Waivers	Members With Waivers	Members Without Waivers	Members With Waivers	Members Without Waivers	Members With Waivers	Members Without Waivers	Members With Waivers	Members Without Waivers	Members With Waivers	Members Without Waivers
	(n=32)	(n=92)	(n=32)	(n=92)	(n=32)	(n=92)	(n=32)	(n=92)	(n=32)	(n=92)	(n=32)	(n=92)
Mean	0.404	0.307	0.413	0.316	0.431	0.340	0.393	0.294	0.378	0.277	0.361	0.268
Variance	0.023	0.025	0.029	0.028	0.022	0.028	0.027	0.026	0.027	0.028	0.022	0.022
Degrees of freedom	56		53		60		53		54		54	
t Statistic	3.057		2.772		2.875		2.974		2.974		3.041	
P(T<=t) two-tail	0.003*		0.008*		0.006*		0.004*		0.004*		0.004*	

Source: Compiled by ERG.

* statistically significant at $\alpha = 0.05$

The expertise index is comprised of a simple average of the following normalized variables:

a) Primary Analysis: years of experience, years of clinical experience, total publications, and H-index.

b) Sensitivity Analysis 1: years of experience, years of clinical experience, and total publications

c) Sensitivity Analysis 2: years of experience, years of clinical experience, and H-index

d) Sensitivity Analysis 3: years of experience, total publications, and H-index

e) Sensitivity Analysis 4: years of clinical experience, total publications, and H-index

f) Sensitivity Analysis 5: years of experience, years of clinical experience, total publications, and total citations

12. APPENDIX D: MEMBERS OF THE SUB-SAMPLE WITH WAIVERS

Meeting Topic	Name	Expertise	Nature of Conflict(s)
Orlistat	Neal L. Benowitz, MD	Pharmacology	Stock (competitor), consulting (sponsor/competitor)
Orlistat, CFCs in MDIs	Terrence F. Blaschke, MD	Pharmacology, drug modeling design	Consulting (company with financial interest)
Genasense, Fragmin, Abraxane	Ronald M. Bukowski, MD	Hematology, oncology	Unrelated consulting (sponsor/competitor), unrelated speaker's bureau
Orlistat	Thomas O. Carpenter, MD	Pediatric endocrinology	Speakers' Bureau (competitor)
Tysabri	Steven T. DeKosky, MD	Alzheimer's, memory disorders	Unrelated consulting and speakers bureau (competitor), unrelated activities for visiting professor program
CFCs in MDIs	Steven E. Gay, MD, MS	Pulmonary, critical care	Speakers' Bureau (affected company)
Tysabri	Larry B Goldstein, MD	Neurology	Unrelated consulting (competitor)
Fragmin, Abraxane	David P. Harrington, PhD	Statistics	Related study (competitor)
Genasense, Fragmin, Abraxane	Pamela J. Haylock, RN	Oncology nursing	Stock (sponsor/competitor)
Genasense, Fragmin, Abraxane	Maha HA Hussain, MD	Hematology, oncology	Stock (sponsor/competitor)
Tysabri	Lily K.F. Jung, MD, MMM	Neuroscience	Speakers Bureau (sponsor/competitor)
Tysabri	Karl D. Kieburtz, MD, MPH	Neuroscience	Unrelated consulting (sponsor/competitor)
Orlistat	Ruth M. Parker, MD	Label comprehension	Co-editor of unrelated journal supplement (competitor)
Genasense, Fragmin, Abraxane	Michael C. Perry, MD	Hematology, oncology	Stock (sponsor/competitor)
Tysabri	Ralph L. Sacco, MD, MS	Neurology, epidemiology	Unrelated consulting (competitor)
CFCs in MDIs	David A. Schoenfeld, PhD	Biostatistics	Unrelated contract (affected company), consulting (affected company)
Orlistat	Alastair J. J. Wood, MD, PhD	Clinical pharmacology	Unrelated consulting (competitor)

13. APPENDIX E: WHAT DOES A 0.09 DIFFERENCE IN OVERALL EXPERTISE INDEX MEAN?

ERG concluded that the members in our sample with waivers had a mean overall expertise index of 0.40 and the members without waivers had a mean overall expertise index of 0.31. This is a difference in mean overall expertise of 0.09. How might we quantify this difference in terms of the individual components of the overall expertise index (i.e., actual years of experience, years of clinical experience, total publications, or H-index)?

In order to address this question, ERG utilized multivariate regression to assess the unit change necessary to increase a member's expertise index by 0.09 for each independent variable (ceteris paribus).

ERG utilized the following regression equation:

$$\text{Expertise Index} = x + ß_1\,(\text{Years of Experience}) + ß_2\,(\text{Years of Clinical Experience}) + ß_3\,(\text{Total Publications}) + ß_4\,(\text{H-index})$$

where the non-normalized (actual) values of the individual variables for each advisory committee member were used. The table below presents the regression coefficients and mean for each variable.

Variable	Regression Coefficient	Mean
Years of Experience	0.007	25.8
Years of Clinical Experience	0.005	17.7
Total Publications	0.0003	170
H-index	0.003	23.8

Since the dependent variable for each observation (expertise index) is calculated as a linear combination (i.e. simple average) of each expert's credentials, the relationship between dependent and independent variables is deterministic, not stochastic. Thus, the linear regression simplifies to a line-fitting exercise with an R-Square equal to one.

Evaluated at the mean for the sample, the following can be inferred from these results:

Holding all else equal, a 0.09 increase in the overall expertise index could be brought about either by:

- An increase in years of experience by 13.7 years; or
- An increase in years of clinical experience by 17.3 years; or
- An increase in total publications of 260; or
- A rise in the H-index of 28.1.

It is important to note that the normalized values for each variable and, therefore, the individual values of the expertise index are sample-dependent. The results presented above are, therefore, also sample-dependent and evaluate the impact of a unit change in each variable at the mean for the group. These results should only be considered in this context. They should not be used to describe the relationship between specific experts or their individual measures of expertise either within the sample or beyond.